Hospital Library

VOLUME LXXIII

NUMBER 6

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

December, 1943

Lewellys Franklin Barker. CHARLES R. AUSTRIAN 401

Mucormycosis of the Central Nervous System. A Report of Three Cases. JOHN E. GREGORY, ALFRED GOLDEN, MAJOR M. C., A. U. S. AND WEBB HAYMAKER, CAPTAIN M. C., A. U. S. 405

The Distribution of Certain Oxidative Enzymes in the Ciliary Body. JONAS S. FRIEDENWALD, M.D., HEINZ HERRMANN, M.D., AND ROBERT MOSES, M.D. 421

Salicylate Therapy in Rheumatic Fever. A Rational Technique. LT. COMDR. ALVIN F. COBURN, (MC) U. S. N. R. 435

On the Anaphylactic Nature of Rheumatic Pneumonitis. ARNOLD R. RICH AND JOHN E. GREGORY 465

Sodium Propionate in the Treatment of Superficial Fungous Infections. EDMUND L. KEENEY, M.D. AND COMDR. EDWIN N. Broyles (MC) U. S. N. R. 479

Book Reviews 488

Index to Volume LXXIII 493

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

COPYRIGHT, 1943, BY THE JOHNS HOPKINS PRESS

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, L. EMMETT HOLT, JR.

ASSOCIATE MANAGING EDITOR, JOHN A. LUETSCHER, JR.

EDITORIAL BOARD

E. Cowles Andrus
Charles R. Austrian
W. Halsey Barker
James Bordley, III
Chalmers L. Gemmill
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore-5, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefor adjusted accordingly.

Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

LEWELLYS FRANKLIN BARKER
1867–1943

LEWELLYS FRANKLIN BARKER

CHARLES R. AUSTRIAN

On July 13, 1943, Dr. Barker, Professor Emeritus of Medicine, died. The immediate successor of Dr. Osler, he was the last survivor of the initial era of the medical department.

Lewellys Franklin Barker was born September 16, 1867, in Milldale, Ontario, Canada, the first child of James Frederick and Sarah Jane Barker. Reared, until the age of sixteen, as a Quaker, he was baptized at seventeen when his father became a convert of the Baptist Church but it was to his Quaker tulelage that he was ever grateful for the examples of living that were set him. He attended public school near Milldale, Pickering College, a Quaker collegiate institute, and then, was apprenticed to the village apothecary, James Gibbard. Two years of apprenticeship served, he was persuaded by his friend James Collier to study medicine and, released by his employer, he entered the University of Toronto, where he helped pay his way by conducting "chemistry grinds" for fellow-students, by winning scholarships and by working as an insurance agent. A shy, sensitive youth, he read widely, shunned metaphysics, displayed an uncommon memory for facts and cultivated a philosophy of life. In 1890, he received the degree of Bachelor of Medicine, was awarded both the University and the Starr Gold Medal, and an appointment as an interne at the Toronto General Hospital where with our Dr. Thomas Cullen he felt the lure of the newly established Johns Hopkins Hospital and wrote to Dr. Osler for a place there. Dr. Osler had no vacancy in his department but offered him the position of Resident Physician for the summer months at the Garrett Hospital for Sick Children located at Mt. Airy, Md., as well as a welcome to attend his rounds at the Hopkins. He accepted both offers and his career in the United States was inaugurated. The residency at Mt. Airy completed, long attendance at clinics would have been impossible for financial reasons had not a chance vacancy at the Johns Hopkins Hospital provided his keep and had not Dr. Osler secured for him editorial work from which he acquired the wherewith to continue in an academic sphere and to develop skills of utility in later years.

For almost nine years, Dr. Barker lived in the hospital, initially as an attendant of medical rounds, in 1892 as Fellow in Pathology, thereafter as Resident Pathologist, as Associate in Anatomy (1893) and as Associate Professor of Anatomy (1897). During those years, close association particularly with Drs. Mall and Welch was responsible in large measure for the shaping of his subsequent career, for from them came not only the stimulus for scientific training but his ideals of medical education. So, too, did intimate working relations with Simon Flexner, Councilman and other members of the original faculty of the Medical School help set his direction, and unhampered by "an undue concern" over the presence of a heart murmur, he was active in research and in teaching.

In 1895, he went to Europe, visited Leipzig where he attended the lectures of His, Wundt and Flechsig, and carried out studies of sensory localization under von Frey, which last included the determination of the disturbances caused by his own cervical rib and helped stimulate the later publication of his admirable book, *The Nervous System and Its Constituent Neurones*. Then, in 1899, with Flexner, Flint, Gay and Garrett, he was a member of a commission that went to the Philippine Islands to study tropical diseases. The following year, he was invited to be Professor of Anatomy at the University of Chicago and, though reluctant to accept the post because his major interest was in clinical medicine, he did so when convinced it was a preparation for the career to which he aspired. From 1900 to 1905, except for a brief period in 1901 when he served as a member of a Federal Commission to study the occurrence of Bubonic Plague in San Francisco, he conducted his department, publishing meantime a translation of Spalteholtz' *Hand Atlas of Human Anatomy*, and *A Laboratory Manual of Human Anatomy*. In 1900, in a lecture at Indianapolis, he stressed the importance of laboratories in connection with hospitals for the insane, and in 1902 he addressed the western alumni of the Johns Hopkins University upon the topic *Medicine and The Universities*. In the former, he advocated a major improvement of American hospital clinics of which he became the initiator, and in the latter, he made that plea for the endowment and organization of clinical departments on a real university basis that, when harkened to later, was to confront him with such a stern dilemma.

In the summer of 1903, he married Miss Lilian Halsey and with her,

a few months later, he left Chicago to spend a year abroad. During this furlough he visited many clinics but spent most of his working time in Munich with Friederich von Müller and in Berlin with Friederich Kraus and Emil Fischer. Shortly after his return, he was made Professor of Medicine at Rush Medical College and then in 1905 he was called to succeed Dr. Osler at the Hopkins. He asked at this time to be placed upon a full-time basis, but was told that no funds were then available for an adequate salary. In the years from 1905 to 1914, he continued the practices of Oslerian initiation, established investigative laboratories in the clinic, developed the physiological-anatomical approach to the study of disease, emphasized the rôle of eugenic, chemical, endocrine, metabolic and psychogenic factors in health and in illness. His knowledge of the structure and functions of the nervous system made him shine as a neurologist; his love of and insight into people fitted him to treat well those designated "neurotic" and theretofore handled so casually; and made him parent of a group of physicians armed with a helpful skill. He chose his associates with care, assigned specific duties to them and then guided or advised but did not directly supervise them. He held to the view that a major degree of autonomy is stimulating: that sub-heads, chosen wisely are to be trusted to do well:—if they do, promote them; if they cannot, replace them. He relied upon his junior staff, demanding punctuality, accuracy, thoroughness and order. He encouraged original thinking and investigative work although his own mind was more encyclopedic than imaginative, unique in its capacity to assimilate, expound and evaluate critically known facts. He was a great teacher in the Chaucerian sense for "gladly wold he lerne and gladly teche." His clinics at bedside or in amphitheatre were models presented with a completeness, clarity and ease of expression rivalled seldom. He practiced and taught industry, system, honesty in work, brevity and unity in presentation. He made at least three real contributions to medicine in this country—first he established here, as had von Müller and von Ziemssen in Munich, special research laboratories as integral parts of the medical clinic; second, he recognized and treated the individual as a unit—a psychobiological unit, and third, he emphasized the importance of group diagnosis.

The years from 1905 to 1914 were happy, busy years for Dr. Barker

for, in addition to his work in the hospital and medical school, he carried on a large consultation practice that was national in its scope, lectured extensively and was active in numerous professional organizations. Many honors came to him including membership in honorary fraternities, the presidency of local and national medical societies and honorary degrees from the University of Toronto (1905), Queen's University, Kingston (1908), McGill University (1911) and University of Glasgow (1930). And then in 1914, with the establishment of the full-time status of the professorship of medicine by the Hopkins he had to choose between the proffered conditions and the resignation of his post. Times and his obligations had changed since he had advocated the inauguration of just such a plan so that, after earnest travail, he felt forced to deny the child of his own creation. With that same strength that enabled him in 1905 to bear with sweetness and apparent unconcern the unvoiced but at times ill-concealed comparison of his clinical activities with those of the "Chief", he carried on as Professor of Clinical Medicine and later as Emeritus (1921). His practice continued to increase; his teaching remained of unaltered quality; he championed as actively as ever his ideas of nomenclature and of "multidimensional diagnosis"; lectured, wrote numerous articles and published several books, among them the three volume *Clinical Diagnosis of Internal Diseases*. Whatever disappointment he may have felt was compensated for by his recognized eminence as teacher, consultant and as citizen. His home life was happy; the sorrow over the loss of two infant children and because of the permanent incapacity of his first-born boy were more than outweighed by the affection and perfect companionship of his wife and by his justifiable pride in his talented daughter and able son.

All who knew Lewellys Barker will long recall his rare personality, his Grecian countenance, the twinkle in his eye, his courtly bearing, grace and ease. And these recollections, enhanced by that of his stoical bearing as he faced the inevitable outcome of his last illness, will be good memories. Truly, as he said in his autobiography he "had a good run" and was willing to call it a day.

MUCORMYCOSIS OF THE CENTRAL NERVOUS SYSTEM

A Report of Three Cases

JOHN E. GREGORY, ALFRED GOLDEN, Major, M.C., A.U.S. and
WEBB HAYMAKER, Captain, M.C., A.U.S.

From The Department of Pathology, The Johns Hopkins Medical School, Baltimore, Maryland, and The Army Medical Museum, Washington, D. C.

Those fungi which make up the group called molds are numerous and heterogeneous. They are characterized by large mycelial threads with numerous branches, aerial hyphae, and the frequent presence of distinctive spore-bearing bodies. Prominent among them are members of the Class *Phycomycetes*. Of this Class the order *Mucorales* contains one family, the *Mucoracea*, which is parasitic in animals and man (1).

The first study of the pathogenicity of the *Mucoracea* was carried out by Lichtheim (2) who described two strains, *Mucor corymbifer* and *Mucor rhizopodiformis*. The spores of these fungi when injected into the blood stream of rabbits produced widespread abscesses which resulted in the death of the animals. Two years later, in 1886, Lindt (3) grew and described two other strains, *Mucor pusillus* and *Mucor ramosus*, which he demonstrated, in a similar manner, to be pathogenic for rabbits.

Spontaneous infections have been reported in birds (4, 5), dogs (6), pigs (7), horses (8, 9, 10), and cows (11, 12, 13). These mucormycoses of animals are of importance since, as is suggested by Castellani (1), they may be transferred to humans. It is interesting that the lesions produced in animals are quite similar in location and in histological characteristics to those reported in man.

Among the recorded human infections, which are scarce, there is but one, that of Paltauf (14), of generalized dissemination of the fungus. In this case the portal of entry was thought to be in the intestine, which contained numerous mural nodules some of which were ulcerated. Many abscesses were found in the mesenteric lymph nodes, lungs and brain. All of the lesions contained hyphae and in the lungs the typical sporangia of *Mucor corymbifer* were found. This case resembles very closely, in suspected portal of entry and in the presence and histological

appearance of intestinal and mesenteric lesions, the nine cases in pigs reported by Christiansen and Nielson (7).

In most of the other reported cases of human infections only a single organ or system is involved. The majority record invasion of either the lungs (1, 10, 20, 21, 22, 23, 25, 26, 27, 28) or of the ears (1, 15, 16, 17, 18, 19), although five reports of gastric ulcers, thought to be due to these fungi, have been found (29, 30, 31, 32, 33). Infection of the nose (10, 39), and skin (34, 35, 36) seem to be quite uncommon. Least often affected is the central nervous system (14, 37). Of the two cases reported only Paltauf's (14) seems well established. Hafstrom, Sjöquist and Henschen (37) found a calcified mass in the brain of a man who had had cerebral symptoms for ten years. Sections of the mass revealed a number of hyphae-like structures. The size of these structures and the presence of a body thought to be a sporangium led the authors to the conclusion that the infecting agent was a *Mucor*.

Freeman (38), in a review of fungus infections of the central nervous system, written in 1932, does not mention the *Mucoracea*.

Recently there have been brought to our attention three very similar cases of Mycormycosis in which the fungi invaded the meninges and brain by way of the orbit.

Case 1 (History No. 102411) is that of a 43 year old colored woman who was admitted to the Johns Hopkins Hospital on February 8th, 1941. She had been comatose for 12 hours. The history obtained from relatives revealed that two years previously she had been found to have diabetes mellitus, but had never taken insulin, nor had she adhered to a restricted diet. In the last few months the patient had complained frequently of excessive thirst and of abdominal pain and nausea. Two or three days before admission she had spoken of pain and loss of vision in her left eye. On the day before she was brought to the hospital she felt ill and stayed in bed. During the evening the patient became unable to talk, began to breathe rapidly and became comatose. On examination, the characteristic signs of diabetic acidosis were found. The blood sugar was 520 mgm. %, the CO_2 combining power 11.7 vol. %, the urinary sugar and acetone 4+. Her total white cell count was 15,700 with 77% neutrophiles, of which 18% were juvenile forms. The blood Wassermann was negative. Although shock and acidosis were successfully combated, she never regained consciousness. In the first few hours her face became edematous, particularly about the eyes. Twelve hours after admission there was noted a triangular area of dark bluish discoloration over the bridge of the nose, about the medial portion of the left eye, and extending to the inner corner of the right eye. This area had a clearly defined, pale margin and was thought to be an infarct. It increased rapidly in size,

so that the whole left eye was involved. The conjunctiva became swollen and discolored. The fundus of this eye was never well seen, due to haziness of the cornea. The right eye, which, until this time, had been practically normal except for arterial tortuosity, showed striking changes. The optic disc was white, as was a large part of the surrounding fundus. The arteries were hardly visible and the veins were beaded. It was thought that these changes indicated thrombosis of the anterior branches of the circle of Willis and of the cavernous sinuses. The patient died approximately 24 hours after admission with a temperature of 105°F.

At autopsy (No. 17262), in addition to the discolored area described above that involved the nose and left eye, the mucous membrane over the left side of the nasal septum and turbinates was blackened and looked necrotic. The heart was somewhat atrophic as were the liver and pancreas. The right kidney was less than one half the size of the left and was considerably scarred. There was erosion of the cervix and a few small, shallow ulcers in the vagina. The meninges over the vertex of the brain were delicate, but over the whole inferior surface they were dull, opaque and blood-stained. This change extended up over the anterior tips of the frontal lobes for a short space. The superficial blood vessels over the left hemisphere were not washed clear of blood by the embalming fluid as were those on the right side. The left cavernous sinus contained a gray thrombus. The left internal carotid artery in the cavernous sinus was completely occluded by a thrombus which extended upward to the circle of Willis and on into the anterior cerebral, the left middle and posterior cerebral and the posterior inferior cerebellar arteries. On section the brain beneath the opaque discolored meninges looked poorly preserved and was soft and crumbled easily. The gray matter had a reddish-black color and the white matter was stained pink, suggesting hemolyzed blood. The depth of these changes was variable, extending at most 2 to 3 cm. toward the ventricles. The tissues in the left orbit were red and soft, while those in the right orbit looked normal.

On microscopic examination there were found hyaline islands of Langerhans in the pancreas with glycogen deposition in the renal tubular epithelium and periportal liver cell nuclei. The kidneys, in addition, contained many moderately sclerotic arteries and parenchymal scars as well as typical lesions of syphilitic focal nephritis. These latter consisted of lymphoid nodules in the interstitial tissue that herniated into the tubulesand obstructed them. Above the point of obstruction the dilated tubules contained granular amorphous debris and many cholesterol crystals (40). In sections of the posterior portions of the eyes, the hypophysis, the left cavernous sinus, the left internal carotid artery, the branches of the circle of Willis mentioned above, and of the meninges and brain there was seen widespread invasion by a fungus. The organism had grown mainly in the blood vessels where masses of branching hyphae embedded in thrombus material often completely filled the lumina and partially replaced the walls. There was considerable necrosis of the brain, apparently due to infarction following this peculiar vascular occlusion. Surprisingly little cellular reaction was seen about the fungi and most of this was in the meninges. Of the cells present, a relatively large proportion were macrophages. Bacterial stains revealed no organisms other than the fungus.

From study of the material at hand, it seems most likely that the infection started in the nose and extended through the angular vein and its branches that reach the orbit and empty into the cavernous sinus by way of the ophthalmic vein. Unfortunately no sections were taken of the nasal mucosa and, of course, none of the face.

The fungus was quite large. Most of the hyphae measured about 18 microns in diameter, but varied from 6 to 50 microns. There were no septa present. Most of the hyphae were long tubes with lateral branches, as is shown in the illustrations (Figs. 1, 2, 4, 5, 11). They were irregular in width with swellings and constrictions scattered along their length. It was not unusual to find, in the stained sections, filaments measuring 150–200 microns in length. Their walls were represented by a single thin line of protoplasmic condensation staining deeply blue, while the cytoplasm stained lighter blue in the hematoxylin and eosin sections. The cytoplasmic material varied in appearance from place to place, but was mostly clear with fine to coarse scattered aggregates of blue-staining granular material.

Case 2 (History No. 152453) is that of a 52 year old colored female who was admitted to the Medical Service of the Johns Hopkins Hospital June 14, 1943, in a comatose state. Her past history revealed that she had been treated for diabetic coma in this hospital in 1938, and again in 1942 in another hospital in the City. In 1938 she had been found to have chronic sinusitis involving the right antrum, frontal and ethmoid sinuses. The antrum was irrigated at that time. Very little could be learned about the recent history. It was said, by her relations, that little insulin and considerable quantities of alcohol had been taken in the last few weeks. For one week before admission the patient complained of abdominal pain and malaise. The day before she was brought to the hospital there was increasing drowsiness which progressed to coma. On examination the usual findings of diabetic acidosis were evident.

The blood sugar was 480 mg. %, the CO_2 combining power 6.5 m. equiv., the urinary sugar, acetone and diacetic acid all were 4+, the white blood count 11,000 per cmm. In addition to the classical physical findings there was proptosis of the right eye and marked conjunctival oedema. These changes increased with improvement of the hydration. The right cornea was clear, the pupil dilated and fixed. The corneal reflex was absent and there was complete external ophthalmoplegia. The eye grounds on both sides looked normal. The nose appeared to be filled with bloody crusts. X-ray examination showed clouding of the right frontal and antral sinuses and of the orbit. The acidosis and dehydration responded well to treatment but the patient never became fully conscious. The increasing proptosis and periorbital edema led observers to the conclusion that there was a cavernous sinus thrombosis. Lumbar puncture revealed increased protein and 150 mononuclear cells per cmm. Cultures of the fluid were sterile. Two days after admission crepitus was felt in the orbit and an aspiration was done. Cl. Welchii grew from cultures of the aspirated material. The patient was taken to the Wilmer Ophthalmological operating room and the right eye was enucleated without anaesthesia. Considerable necrosis of the orbital tissue was found with osteomyelitis of all the bony plates forming the medial borders of the cavity. Portions of the

nasal bone and its covering tissues were removed. Sections of this material showed it to be invaded by a large fungus as well as Cl. Welchii. The enucleated eye itself was free of such invasion. By the fourth hospital day there had developed clear signs of meningitis and a lumbar puncture obtained spinal fluid which contained 295 cells per cmm. of which 80% were polymorphonuclears. Cultures of the fluid were again sterile. The patient died on the fifth hospital day with a terminal rise of temperature to 105°F.

At autopsy (No. 18421) the right upper half of the face was found to be quite edematous. The right eye had been removed surgically. The cavity remaining was lined by dark, blood-stained, malodorous tissue. After the brain was removed purulent material was seen beneath the dura on both sides of the crista galli. Pressure in the right orbit caused the exudate to well up from the ethmoid sinuses. When these sinuses were unroofed it could be seen that the entire cavity connected with the nose and the whole space was lined by black, apparently necrotic, material continuous with that in the right orbit. On the inferior surfaces of the frontal lobes of the brain the tissue was destroyed and ragged. The necrotic area was about 4 cm. wide on each side and extended backward for approximately 5 cm. Cross sections after the brain was hardened showed that the destructive process extended inward as far as the corpus callosum in places. Elsewhere the meninges were delicate except for a pool of purulent material in the cisterna magna. Further sections of the brain revealed two or three small, smooth-walled cavities, each 2–4 mm. in diameter in the white matter of the right hemisphere. They looked like the gas bubbles so commonly produced by postmortem growth of Cl. Welchii. None of the dural sinuses contained thrombi. In addition to these changes there was found a large, irregular, V-shaped scar in the right kidney that on section appeared to be an old healed infarct. The body and tail of the pancreas were markedly reduced in size and were scarred, although the head of this organ looked normal. There were numerous pleural and pelvic adhesions and a small right hydrosalpinx.

Study of the microscopic sections revealed profuse growth of a fungus identical morphologically with that described in Case 1. This fungus was found in the following tissues: the material removed from the nose at operation, the ethmoid air cells, the ocular muscles and surrounding tissues, and the frontal lobes of the brain. Most striking, however, was the growth of this organism in the walls and lumina of orbital and cerebral blood vessels. Undoubtedly most of the necrosis observed in all the tissues mentioned was due to the vascular occlusion thus produced. The amount of cellular exudation varied from place to place, being moderate in the nasal and orbital tissue and quite marked in the brain. The cells were largely polymorphonuclear leucocytes but there were numbers of macrophages and lymphocytes. It seems apparent that the leucocytic reaction was called forth largely by necrotic tissue, for the mere presence of the fungus did not do so (Fig. 4). In view of the profound edema and necrosis of the ocular muscles, which were filled with hyphae, it is small wonder that there was complete external ophthalmoplegia. Neither the eye removed at operation nor the remaining one taken out at autopsy

were invaded. Numerous Cl. Welchii were seen scattered through the tissues of the orbit. Consideration of the late and small amount of gas formation and of the presence of hyphae in large numbers in the deeper tissues where no Welch bacilli were seen, leads one to conclude that the latter organism was a secondary invader.

In addition to the changes described there were found scattered hyaline islands of Langerhans in the pancreas, heavy deposition of glycogen in the renal tubular epithelium and a moderate amount of pulmonary edema.

Case 3. Army Medical Museum Accession 87679 (Contributed by the Washington Sanitarium and Hospital, Takoma Park, Maryland).

This 75 year old obese white male was admitted to the hospital by ambulance on December 22, 1942, in a confused mental state. The only information elicited from the patient was that he felt very tired. Physical examination revealed a protruding right eye and a bulging conjunctival sac. The right side of the face was relaxed and the corner of the mouth was drawn to the left. The extremities showed coordinated movements. There was urinary incontinence. Physical examination of the lung fields and of the cardiovascular system revealed no abnormalities. The clinical impresssion at the time of admission was cerebral hemorrhage on the basis of arteriosclerosis. Several hours after admission the patient developed Cheyne-Stokes respiration. It was noted at this time that the right eye did not respond to light and that the pupil was fixed in mid-dilatation while the left eye reacted normally. The next morning his condition remained unchanged but during the day there was no return of consciousness. The patient sank deeper into coma and died at 9.30 a.m., on December 24, 1942.

At autopsy the right pupil was slightly larger than the left and there was marked proptosis of the right eye with associated congestion and bullous edema of both the ocular and palpebral conjunctivae. There were patchy hemorrhages and congestion in the lungs. The heart was enlarged, weighing 510 grams. The liver showed well marked nodular cirrhosis. There was considerable separation of the pancreatic lobules by fat. The intrarenal arteries showed moderate sclerosis and there was fine diffuse scarring of the kidneys. The superficial blood vessels of the brain were congested throughout. Repeated coronal sections of the brain revealed numerous focal hemorrhages, chiefly in the mid portion of the pons on the left. The right eye and retrobulbar tissue looked grossly normal.

On microscopic examination there was seen congestion of the lungs with patchy edema and emphysema, nodular cirrhosis, interstitial fatty infiltration and scarring of the pancreas as well as scattered hyalinized islands of Langerhans, heavy glycogen deposition in the epithelium of the loops of Henle in the kidney and in the liver cell nuclei, arterio- and arteriolosclerosis of the kidneys. A fungus identical with that described in Cases 1 and 2 was found in the cornea, sclera, ciliary body, and choroid of the right eye as well as in the optic nerve and episcleral tissues. Hyphae were also seen in the central nervous system in three areas: the meninges surrounding the cerebellopontine angle and the adjoining medulla oblongata and cervical cord, the capsule and extracapsular tissue of the hypophysis and the meninges in the region of the left rhinal sulcus. The meningeal vessels, especially the veins, were

greatly distorted and were heavily infiltrated with lymphocytes and polymorphonuclear leucocytes as well as numerous hyphae. The lumina of these vessels were partly filled with inflammatory cells and hyphae. The pons was the most severely involved part of the brain. Scarcely a low power field of the left side was free of hyphae and associated miliary foci of inflammatory cells. Many of the vessel walls were partly necrotic and were heavily invaded by the fungus and leucocytes.

The tendency to invade the blood vessel walls and to grow in their lumina seems to be a very common one in infections with this fungus. It was seen in all three of the cases reported here, and is specifically recorded many times in the literature (14, 26, 30, 31, 32).

Discussion

In none of the cases presented were cultures of the fungus obtained. Complete identification under these circumstances is impossible. Partial identification is difficult and to be attempted only by an expert. The sections from these cases as well as portions of the gross material were consequently sent to Dr. C. W. Emmons, Principal Mycologist of the United States Public Health Service. Dr. Emmons has been kind enough to allow the use of the following quotation from his letter:

"In the absence of a living culture exact identification of the fungus is not possible. The large diameter of the hyphae, the manner of branching and the coenocytic structure are characteristics of the *Mucoracea*. It is probable that this is a species of *Mucor* or a closely related form. The reports of infections caused by *Mucor* are in some cases incomplete and unsatisfactory, but a few species, notably *M. corymbifer* (*Lichtheimia corymbifera*) are pathogenic."

Comparison of the fungus with many descriptions and illustrations contained in the literature further strengthens this partial identification.

Fungus infections of the central nervous system while not extremely rare are nevertheless uncommon. In 17,400 autopsies at the Johns Hopkins Hospital only 10 cases are recorded. Of these 6 are due to torulosis, 3 to actinomycosis and 1 to coccidiosis. Freeman (38) has studied altogether but 25 such infections. Only one of his cases, an infection with aspergillus, was due to a mold fungus. Castellani (1) has written: "Fungi may attack any organ and system of the human body, the integumentary system being the most frequently and the nervous system the most rarely affected."

As mentioned above, there is recorded in the literature only one other well founded case of mucormycosis of the central nervous system. That case was due to the formation in the brain of metastatic abscesses from visceral lesions. So far as can be found the three present cases are the only ones in which there was direct invasion of the meninges and brain. All of them appear to have gained entry by way of the orbit, and it seems most likely that the infections arose in the nose or paranasal sinuses. In Cases 1 and 3 the eye on the involved side was also invaded to a considerable extent, while that in Case 2 was not.

It is important to determine, if possible, the source of these infections. Emmons (42) has written: "By ingestion and inhalation into the upper respiratory passages the individual is frequently exposed to spores of many species of fungi. . . . A few fungi live habitually (usually in the role of harmless saprophytes) on the skin and mucous membranes of man. Some of these fungi are capable under exceptional circumstances . . . of becoming pathogens of man."

The *Mucoracea* are widespread in nature, living as saprophytes or parasites on many plants and animals (41). The possibility of transmission from infected animals has been mentioned previously. Under these circumstances the presence of the fungi in these cases, while fortuitous, is understandable.

In a study of the fungi present in the nose and throat, Motta (39) made cultures on a series of 110 patients. Of these 36 were normals and 74 were diseased. The types of diseases in the latter group were not stated. In this study he was able to grow strains of *Mucor* on two occasions, both from the "diseased" group.

Granting the accidental presence of the fungus on the mucous membranes of the present cases, its devastating attack on the tissues remains to be explained. Gukelberger (28), in reporting a case of *Mucor* infection of the lungs, stated his belief that the diabetes from which his patient was suffering had so lowered the resistance that infection with a usually saprophytic organism had become possible.

That diabetes does decrease resistance to various infections is well known (43), as is the high incidence of fungus infections in diabetics (43).

Two of the patients in this report (Cases 1 and 2) were known diabetics, both in acidosis and coma at the time of admission to the

hospital. The third patient (Case 3) was in a confused mental state on admission and shortly became comatose. The historical data are few in this case and the diagnosis of diabetes mellitus was not entertained by the physicians in charge. Since the patient was incontinent no urine sugar determination was done. There can be little doubt, however, from the microscopic study of the tissues, that he was a diabetic. The presence of hyaline islands of Langerhans in the scarred pancreas, coupled with fairly heavy glycogen deposits in the liver cell nuclei and renal tubular epithelium, constitute evidence universally accepted as denoting, in a patient of this age, the presence of diabetes mellitus (44).

Careful study of these patients reveals no common etiologic factor other than the presence of severe diabetes mellitus.

SUMMARY

Three strikingly similar cases of mucormycosis of the meninges and brain, entering by way of the orbit, are reported. The presence of uncontrolled diabetes, common to all three, is noted and its etiologic significance is discussed. The literature recording infections with this family of fungi is cited. Only one previous instance of involvement of the central nervous system has been reported.

REFERENCES

1. CASTELLANI, A.: *Fungi and Fungus Diseases.* American Medical Association, Chicago, 1928.
2. LICHTHEIM, L.: Ueber pathogene Mucorineen und die durch sie erzeugten Mykosen des Kaninchens. *Ztsch. f. klin. Med.*, **7**, 140, 1884.
3. LINDT, W.: Mitteilungen über einige neue pathogene Schimmelpilze. *Arch. f. exp. Path. u. Pharm.*, **21**, 269, 1886.
4. BOLLINGER: Ueber Pilzkrankheiten höher und niederer Thiere. *Aerztl. Intell.-Blatt*, H. 9–11, 1880, quoted by Paltauf (14).
5. BOLLINGER: *Zur Aetiologie den Infectionskrankheiten mit besonderer Berücksichtigung der Pilztheorie.* Munchen. 1881. Quoted by Hückel (17).
6. RIVOLTA: Giorn. d. anat. fisiol. e patol. degli Animali. 1885. Quoted by Christiansen and Nielson (7).
7. CHRISTIANSEN, M. AND NIELSON, N.: Mucormykose beim Schwein. *Virchow's Arch.*, **273**, 829, 1929.
8. NIELSON, M.: Skimmelvegetation i Kindhulen hos en Hest. *Maanedsskrift f. Dyrlaeger*, **14**, 622, 1902.
9. FRANK, A.: Eine Mykotische neubildung am Widerrist des Pferdes. *Wochenschr. f. Thierh. u. Viehz.*, **34**, 13, 1890.

10. LUCET, A. AND COSTANTIN: Contributions a L'Etude Des Mucorineés Pathogènes. *Arch. de Parasitologie*, **4,** 363, 1901.
11. SMITH, THEO: Mycosis of the Bovine Fetal Membranes due to a Mould of the Genus Mucor. *J. Exp. Med.*, **31,** 115, 1920.
12. GILMAN, H. L., AND BIRCH, R. R.: A Mould Associated with Abortion in Cattle. *Report of the New York State Veterinary College*, p. 127, 1924–1925.
13. BENDIXEN, H. C. AND PLUM, N.: Schimmelpilze (Aspergillus Fumigatus und Absidia Ramosa) als Abortusursache beim Rinde. *Acta Path. et Microbiol. Scand.*, **6,** 252, 1929.
14. PALTAUF, A.: Mycosis Mucorina. *Virchow's Arch.*, **102,** 543, 1885.
15. BÖKE, J.: Zwei Fälle von Pilzwucherung am Trommelfelle (Myringomykosis). *Ungar. Med.-Chirurg Presse.* 1869. Quoted by Podack (23).
16. SIEBENMANN, F.: *Die Schimmelmykose des Menschen Ohres.* Wiesbaden, 1889. Quoted by Lucet and Costantin (10).
17. HÜCKEL, A.: Zur Kenntnis der Biologie des *Mucor Corymbifer*. *Beitr. z. path. Anat. u. allg. Path.*, **1,** 115, 1886.
18. JAKOWSKI, M.: Otomycosis mucorinea (*Mucor Ramosus, Lindt*). *Gazeta Lekarska*, **34,** 1888. Quoted by Podack (23).
19. GRAHAM, H.: *Mucor Corymbifer* in the External Auditory Meatus. *Lancet*, **2,** 1379, 1890.
20. COHNHEIM: Zwei Fälle von Mykosis der Lungen. *Virchow's Arch.*, **33,** 157, 1865.
21. FURBRINGER, P.: Beobactung über Lungenmykose beim Menschen. *Virchow's Arch.*, **66,** 330, 1876.
22. HERLA: Note sur un cas de Pneumomycose chez l'homme. *Acad. roy. Med. Belg.* Brussels, 1895. Quoted by Wätjen, J.: *Henke-Lubarsch*, Vol. 3, p. 485, Berlin, 1931.
23. PODACK, MAX.: Zur Kenntnis der sogenannten Endothelkrebs der Pleura und der Mucormykosen in menschlichen Respirations-apparate. *Deutsches Arch. f. klin. Med.*, **63,** 1, 1899.
24. STICKER, G.: Schimmelpilzerkrankungen der Lunge. *Nothnagels Spezielle Pathologie und Therapie.* Bd. 14, 156. Wien, 1900.
25. ERNST, H. C.: A case of Mucor Infection. *J. Med. Res.*, **39,** 143, 1918.
26. LANG, F. J. AND GRUBAUER, F.: Über Mucor und Aspirgillusmykose der Lunge. *Virchow's Arch.*, **245,** 480, 1923.
27. WÄTJEN, J.: Mucormykose der Lunge. *Klin. Wschr.*, **8,** 280, 1929.
28. GUKELBERGER, M.: Pneumomykosis Mucorina als Sekundärinfection einer Bronchopneumonie. *Deutsches Arch. f. klin. Med.*, **182,** 28, 1938.
29. MARCHAND, F.: Ein eigentümlicher Magenbefund (Ulcus gangraenosum durch Fadenpilzwucherung) nach Vergiftung durch verdorbene Steinpilze. *Verh. d. deutsch. Path. Gesellsch.*, **14,** 183, 1910.
30. BENEKE, R.: Ein Fall von Schimmelpilzgeschwür in der Magenschleimhaut. *Frank. Ztschr. f. Path.*, **7,** 1, 1911.

31. LJUBIMOWA, W. J.: Ein Fall von Ulcus ventriculi verursacht durch Schimmelpilze. *Virchow's Arch.*, **214,** 432, 1913.
32. TEUTSCHLAENDER, O.: Mucormycose des Magens. *Mitteil. a. d. Grenz. d. Med. u. Chir.*, **29,** 1916–1917.
33. LÖHLEIN, M.: Über Schimmelmykosen des Magens. *Virchow's Arch.*, **227,** 86, 1920.
34. (A) SUTHERLAND-CAMPBELL, H.: Paronychia. *Arch. Derm. and Syph.*, **19,** 233, 1929.
(B) SUTHERLAND-CAMPBELL, H. AND PLUNKETT, O. A.: Mucor Paronychia. *Ibid.*, **30,** 651, 1934.
35. WADE, J. L., AND MATTHEWS, A. R. K.: Cutaneous Mucor Infection of the Face. *J. A. M. A.*, **114,** 410, 1940
36. PIRILA, P.: Eine Mucormykose der äusseren Genitalien. Über die Schimmelpilze als Ursache von Hautkrankheiten. *Acta Dermato-Vener.*, **22,** 377, 1941.
37. HAFSTRÖM, T., SJÖQUIST, O., AND HENSCHEN, F.: Zur Kenntnis der Mykotischen Veränderungen des Gehirns. *Acta. chir. Scand.*, **85,** 115, 1941.
38. FREEMAN, W.: Fungus Infections of the Central Nervous System. *Ann. Int. Med.*, **6,** 595, 1932–1933.
39. MOTTA, R.: Sui miceti della cavità nasali e della golla in condizioni normali e patologiche. *Bull. e atti della reale accad.* Med. di Roma, **4,** 240, 1929.
40. RICH, A. R.: The Pathology of Nineteen Cases of a Peculiar and Specific Form of Nephritis Associated with Acquired Syphilis. *Bull. Johns Hopkins Hosp.*, **50,** 357, 1932.
41. CASTELLANI, A. AND CHALMERS, A. J.: *Manual of Tropical Medicine.* London, Bailliere, Tindall and Cox, 973, 1919.
42. EMMONS, C. W.: Medical Mycology. *Botan. Rev.*, **6,** 474, 1940.
43. JOSLIN, E. P.: *The Treatment of Diabetes Mellitus.* Phila., Lea and Febiger, pp. 410 and 459, 1937.
44. WARREN, SHIELDS: *The Pathology of Diabetes Mellitus.* Phila., Lea and Febiger, p. 91, 1938.

EXPLANATION OF ILLUSTRATIONS

(Photographs of Cases 1 and 2 by Miss Dorothy Schmitt)

FIG. 1. Left anterior cerebral artery of Case 1. A large hypha has almost replaced the wall on the right side. Numerous hyphae fill the lumen.

FIG. 2. Episcleral tissue of Case 1. Long hypha at the left. About the artery at the lower right are numerous hyphae cut in cross section.

FIG. 3. High magnification for detail of hyphae in meninges of Case 1.

FIG. 4. Brain of Case 1. There is no inflammatory reaction about the hypha. Note the typical branching.

FIG. 5. Tissue from the right ethmoid sinus of Case 2.

FIG. 6. Orbital muscle from Case 2. Widely separated muscle fibers are marked *a*, the hyphae *b*.

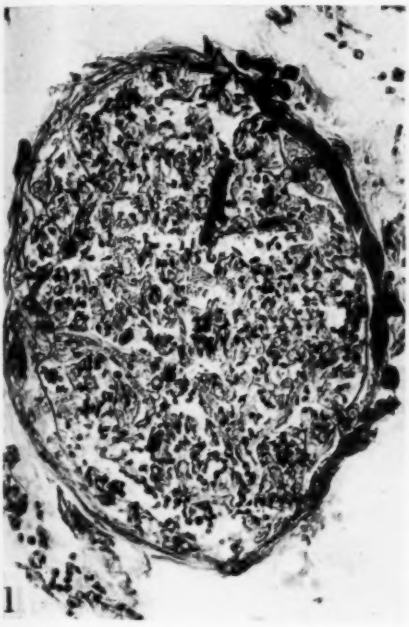
FIG. 7. Orbital blood vessel from Case 2. Hyphae almost fill the lumen.

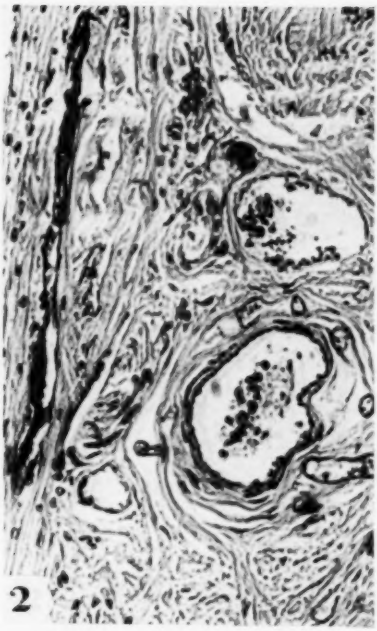
FIG. 8. Cornea of right eye in Case 3. Fungus forms are lying between corneal lamellae (a). Army Medical Museum negative #75866.

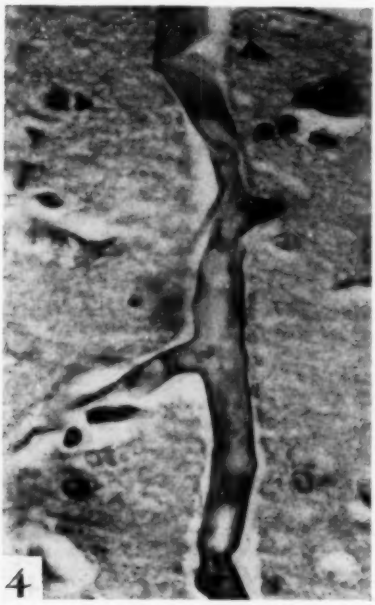
FIG. 9. Pons of Case 3. Inflammatory foci consisting predominantly of polymorphonuclear leucocytes. A filament of the fungus is seen in the center. Army Medical Museum negative #75870.

FIG. 10. Lower medullar oblongata and meninges of Case 3. Army Medical Museum negative #75615.

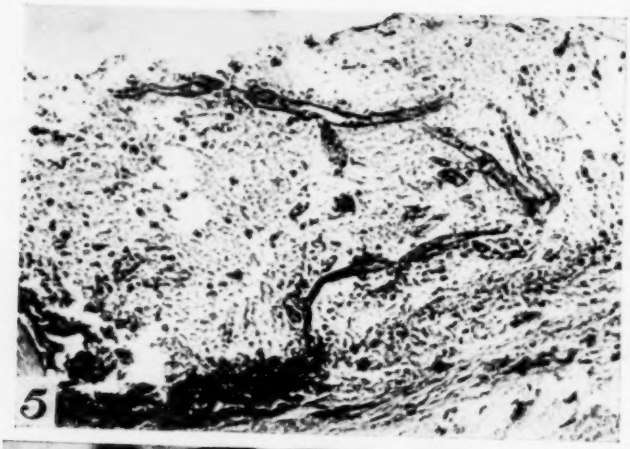
FIG. 11. Edematous and distorted meningeal blood vessel from cerebellopontine angle of Case 3. A long hypha lies in the vessel wall and lateral branches extend into the lumen on the left. Army Medical Museum negative #75614.

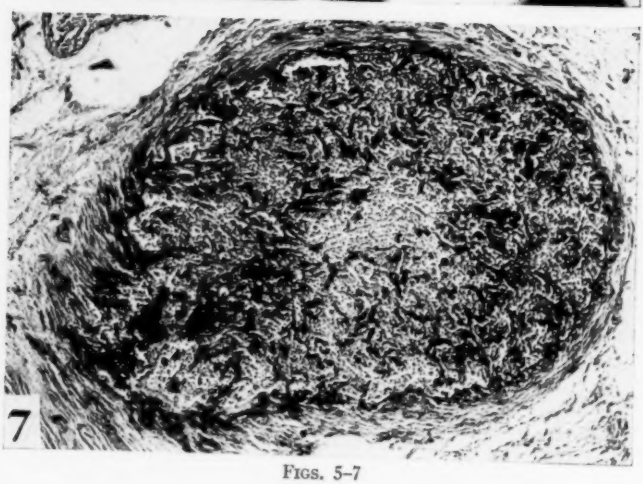






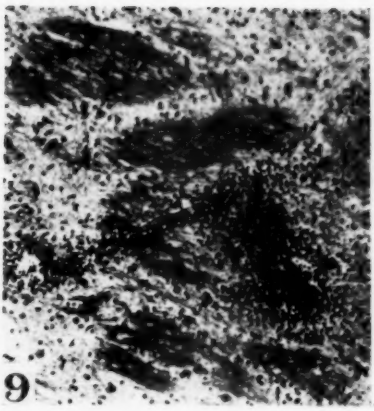
FIGS. 1–4





FIGS. 5–7

8



9

10

11

FIGS. 8–11

THE DISTRIBUTION OF CERTAIN OXIDATIVE ENZYMES IN THE CILIARY BODY[1, 2]

JONAS S. FRIEDENWALD, M.D., HEINZ HERRMANN, M.D., AND ROBERT MOSES, M.D.

In previous reports (1) it has been shown that the secretory activity of the ciliary processes is dependent upon the oxidative interaction of its two tissue components,—epithelium and stroma,—acting across a membrane or barrier that lies between them. Results of various experimental approaches indicated that molecular oxygen does not react directly with constituents of the stroma except possibly to a very minor degree but that the epithelium is the main site of those enzymes, chiefly cytochrome oxidase, which react with molecular oxygen. In the previous studies, the evidence for the presence of cytochrome oxidase in the epithelium and for the absence of this enzyme from the stroma was of an indirect nature. In the present study we have attempted to measure the activity of this enzyme system in the tissue components quantitatively and by direct methods.

As a preliminary step in this study, it was necessary to develop a method for separating the epithelium from the stroma of the ciliary body. In related studies on the chorioid plexus (2) it had been found possible to shake off the epithelium by simple mechanical agitation of the tissue in appropriate suspension fluids. When this procedure was applied to the ciliary tissue it was found that the epithelium came off, not rapidly in large sheets, but slowly in cell fragments. We were forced, therefore, to develop and standardize the separating procedure in considerable detail.

DISSECTION OF CILIARY PROCESSES

Beef eyes, freshly obtained from the slaughter house, are cleansed of conjunctiva, opened equatorially, and the vitreous and lens carefully removed. It is necessary that the zonular fibers of the suspension ligament of the lens should be completely removed from the coronal region of the ciliary body since otherwise they interfere with the des-

[1] From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Johns Hopkins Hospital.

[2] This work was supported in part by the John and Mary Markle Foundation.

quamation of the epithelium in the subsequent procedures. The anterior segment is then everted and pinned down to a dome shaped piece of cork. On careful inspection, a shallow sulcus is to be seen in the surface of the ciliary body just behind the ciliary processes. The point of a scissors is inserted into this sulcus and, following the path of the sulcus a shallow cut not including the ciliary muscle is carried around the whole ciliary body. After this cut has been made, the pars plana can be pushed away from the coronary portion by gentle blunt pressure. A radial incision is now made between two ciliary processes. By careful blunt dissection pushing the coronal tissue posteriorly, a cleavage plane is found such that the whole ring of ciliary processes comes off in a single strip (Fig. 1). The plane of cleavage is in the stroma beneath the ciliary processes and at a little distance from the

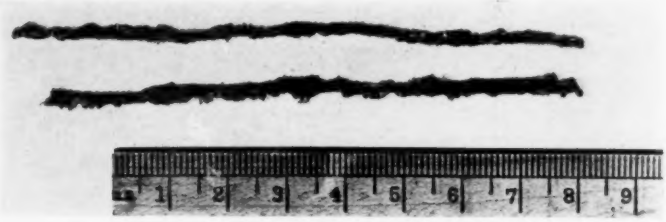


FIG. 1. EXCISED CILIARY PROCESSES FROM BEEF EYES

ciliary muscle. The muscle is therefore not included in the strip. A considerable number of large vessels are to be found in the cleavage plane and their presence may explain the diminished resistance of the tissue in this plane (Fig. 2, 3). While much of the stroma of the ciliary body remains behind in this dissection, the stroma of the ciliary processes and that portion closest to the ciliary epithelium in the valleys between the processes is removed as part of the specimen. These are the portions of ciliary stroma which we have assumed are most directly concerned in the secreting mechanism.

REMOVAL OF EPITHELIUM

The ciliary strips are placed in small flat bottom 5 cc. bottles together with 2 cc. of suspension fluid (see below), and introduced into the stirring machine shown in Figure 4 which was designed for this

purpose by one of us (R. M.). With this device, a bent glass rod is twirled regularly to and fro in the bottle stirring the preparation. Under the influence of this stirring, the epithelial cells and cell fragments

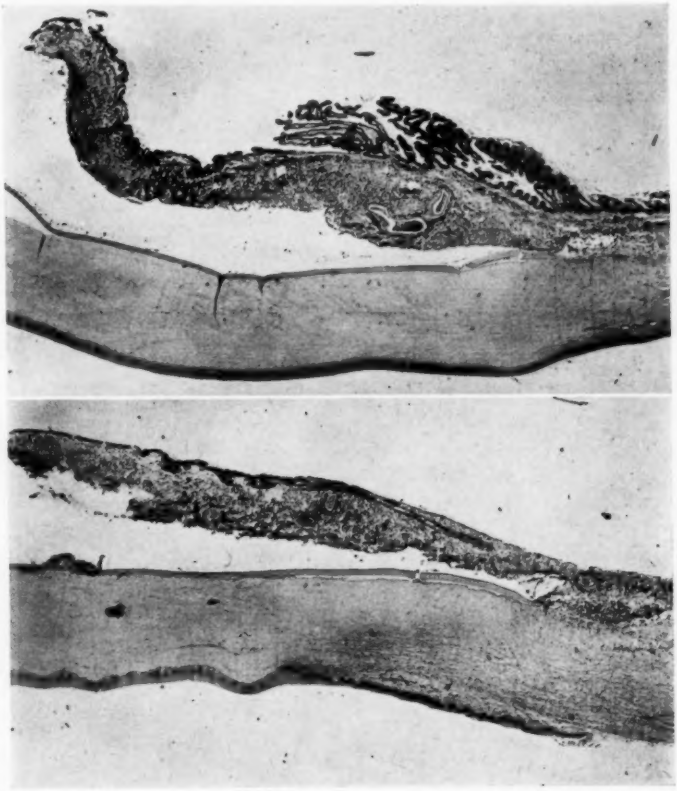


FIG. 2. SECTION THROUGH PART OF THE BEEF EYE
(Upper) Before removal of the ciliary processes
(Lower) After removal of the ciliary processes

flake off from the tissue and are suspended in the fluid. Preliminary experiments showed that a stirring rate of one oscillation per second, each half oscillation consisting in three full turns of the stirring rod, yielded

the most rapid separation of the epithelium without tearing the stroma into fragments. Every 15 minutes, the stirring is stopped, the suspension fluid poured off, the remaining tissue washed with fresh portions of suspension fluid. These washings are added to the suspension fluid in a centrifuge tube and the epithelial cell fragments are recovered

FIG. 3. EQUATORIAL CROSS-SECTION OF CILIARY BODY WITH PROCESSES PARTIALLY REMOVED.

St = Deeper stroma layer
M = Ciliary muscle
Sc = Sclera
Z = Zonula fibers

by centrifuging at 3000 RPM for 5 to 7 minutes. A fresh 2 cc. portion of suspension fluid is added to the tissue and the stirring process repeated.

The first few yields of suspension fluid are inky black with melanin granules. Later yields are gray and composed of a granular debris

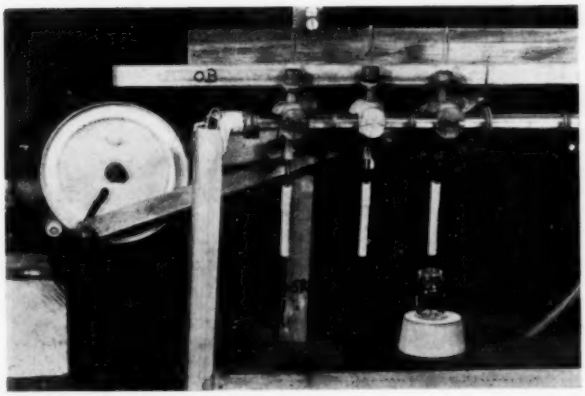


FIG. 4. MECHANICAL STIRRER FOR SEPARATION OF EPITHELIUM AND STROMA OF CILIARY PROCESSES (2.5 OF NATURAL SIZE)

OB = Oscillating beam
SR = Stirring rods
TB = 5 cc. bottle for tissue sample inserted in rubber stopper

FIG. 5. CROSS-SECTION THROUGH STROMA PORTION OF CILIARY PROCESSES AFTER REMOVAL OF EPITHELIUM

with decreasing amounts of pigment and are presumably derived chiefly from the basal layer of epithelial cells. Finally, the granular

debris disappears and the fluid is found to contain only a few fibers. The latter are apparently derived from the stroma since they continue to appear in the suspension fluid however long the stirring is continued. In any case the amount of material represented by these fibers is very small in comparison to the earlier granular yield. The final fibrous yield is taken as the end point of the separating process. Histological study of the remaining tissue at this time shows it to be composed of

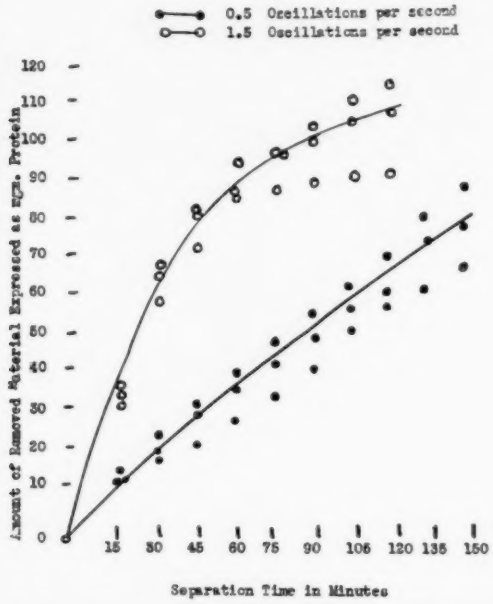


FIG. 6. SEPARATION AT VARYING OSCILLATION FREQUENCIES

reasonably intact stroma with only minimal fragments of epithelium still adhering (Fig. 5).

The course of the separation process can be followed by chemical estimation of the amount of protein in the various portions recovered. Also, the amount of protein in the supernatant fluid after the cell fragments had been centrifuged off can be measured. The results of some of our experiments in this respect are seen in Figures 6–9. The separation is more rapid with a high than with a low speed of stirring (Fig. 6).

It is more rapid in distilled water than in physiologic saline and still slower in hypertonic solutions. The amount of solid matter finally recovered with distilled water as suspension fluid is, however, less than in saline solutions since more of the protein dissolves in the fluid. Variation in pH has little effect on the rate of separation, but somewhat more material goes into solution at high than at low pH within the

TABLE I

Test of Reproducibility of Separating Process Carried out on Paired Samples under Controlled Conditions

Suspension fluid: M/15 Na_2HPO_4 + M/15 KH_2PO_4—pH 6.8. Amount of removed material in mgm. protein for each 15 minute stirring period.

SAMPLE A	SAMPLE B
28.2	27.9
22.6	20.4
20.3	20.6
10.2	12.3
3.3	4.5
3.1	2.9
3.2	2.4
2.2	1.4
93.1*	92.4*
36.0†	33.6†
44.0‡	41.0‡

* Total epithelium.
† Total stroma.
‡ Extract.

range studied. When the factors of oscillation rate, salt concentration, and pH are carefully controlled, the successive yields from two samples show remarkably close agreement (Table I).

DISTRIBUTION OF CYTOCHROME OXIDASE

Having available this standardized method of separating epithelium from stroma, we could proceed to estimate enzyme activity in various fractions. The present report is concerned with the study of the

cytochrome oxidase system along lines similar to those which we have previously reported in regard to the chorioid plexus (2).

TECHNIQUE FOR MEASURING CYTOCHROME OXIDASE

The oxidase activity is measured manometrically. The tissue is ground in a glass mortar in a buffer solution (one part Ringer's Solution, one part N/10 phosphate buffer pH 7.2), in general using 1 cc. of solution per ciliary body. One cc. of the resulting suspension is pipetted into the main chamber of a Warburg flask, and 1 cc. of buffer solution added plus varying amounts of a 1% cytochrome c prepared from heart muscle (4). Solutions of the substrate are adjusted to pH 7.2 and placed into the side arm, 0.15 cc. of 20% NaOH in the central well. The water bath temperature is adjusted to 37.5°C. After thermoequilibrium has been reached, the oxygen uptake is observed for a preliminary period of 10 minutes, then the substrate solution is tipped into the main chamber and the subsequent oxygen uptake recorded.

RESULTS

1. Identification of Cytochrome Oxidase

Figure 7 shows the oxygen uptake of ground ciliary process tissue with various substrates, with and without added cytochrome c. The fact that in every case the oxygen uptake is greater in the presence of cytochrome c is evidence that the oxidizing enzyme is, in fact, cytochrome oxidase. The dependence of the O_2 uptake of such tissue suspension on the amount of cytochrome c added is shown in Figure 8. It should be noted that, as compared with somewhat purified cytochrome oxidase preparations (5, 6), relatively large amounts of cytochrome c must be added to the ciliary tissue to obtain the maximum rate of oxidation.

In order to make the identification of the oxidase more specific, the enzyme was prepared from ciliary tissue by a method similar to that used by Keilin and Hartree (7) for heart muscle.

8 grams of ciliary processes, obtained from 30 beef eyes, were ground with 4 grams of fine sand in 8 cc. of phosphate buffer pH 7.2, for 1½ hours in a glass mortar. Sedimentable material was removed by centrifugation at 3000 RPM for 10 minutes. The cloudy supernatant

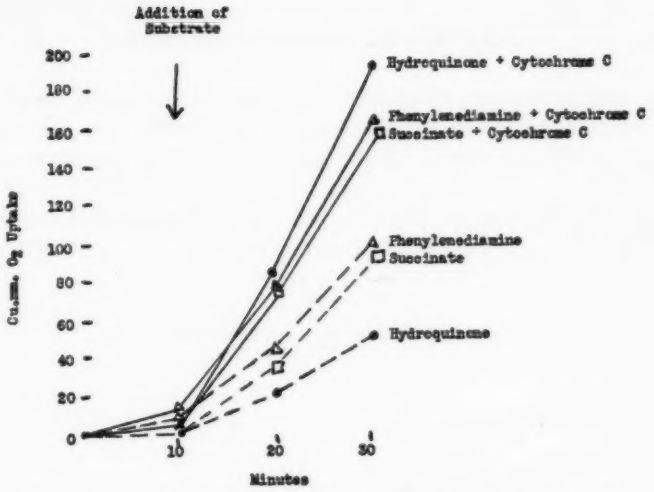


FIG. 7. OXIDATION OF VARIOUS SUBSTRATES BY A SUSPENSION OF CILIARY PROCESSES WITH AND WITHOUT ADDITION OF CYTOCHROME C

Content per flask: tissue 45 mgm. dry weight; Cytochrome c 0.7 cc. 1% solution; substrate 10 mgm. Hydroquinone, 10 mgm. Phenylenediamine, 25 mgm. Succinate dissolved in 0.5 cc. distilled water.

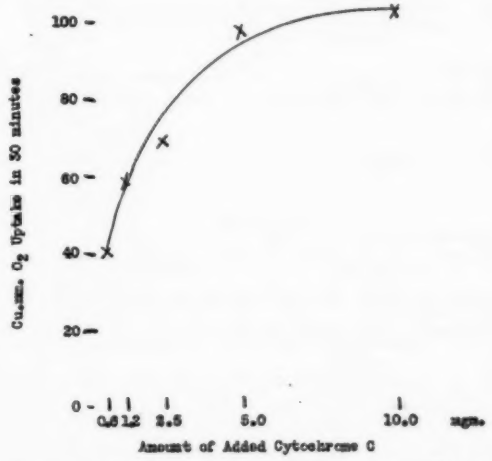


FIG. 8. DEPENDENCE OF O_2 UPTAKE OF A SUSPENSION OF CILIARY PROCESSES UPON CYTOCHROME C CONCENTRATION

Content per flask: fluid volume 3.5 cc.; substrate 10 mgm. Hydroquinone; tissue 20 mgm. dry weight

fluid was transferred to another centrifuge tube, brought to pH 4.5 with glacial acetic acid. The resulting precipitate was centrifuged down and the supernatant fluid discarded. The precipitate was suspended in 20 cc. N/10 phosphate buffer of pH 7.3. One cc. of this suspension was used per Warburg flask with the usual addition of cytochrome c (0.7 cc. of a 1% solution) and substrate (25 mgm. succinate,

TABLE II

Oxygen Uptake of Cytochrome Oxidase Prepared from Ciliary Body by Method of Keilin and Hartree

SUBSTRATES	O_2 UPTAKE IN 30 MIN.
	c.mm.
Catechol	18
Catechol + cytochrome c	90
Adrenalin	18
Adrenalin + cytochrome c	191
Dioxyphenylalanine	6
Dioxyphenylalanine + cytochrome c	85
Hydroquinone	24
Hydroquinone + cytochrome c	175
p-Phenylenediamine	18
p-Phenylenediamine + cytochrome c	204
Ascorbic acid	19
Ascorbic acid + cytochrome c	120
Succinate	26
Succinate + cytochrome c	109

10 mgm. hydroquinone, 10 mgm. phenylenediamine). Table II shows the oxygen uptake with various substrates.

2. Distribution of cytochrome oxidase

If the epithelium is separated from the stroma using distilled water as suspension fluid with the stirring method outlined above, the separation is rapid and reaches a sharp end point. When the tissue components separated in this fashion are tested for cytochrome oxidase

TABLE III

Distribution of Oxidase in Epithelium and Stroma

The amount of tissue used corresponds to 0.5 grams of the fresh unseparated tissue in each flask. Reagents added per flask: 0.7 cc. 1% cytochrome c, 25 mgm. succinate, 5 mgm. hydroquinone and 5 mgm. phenylenediamine.

DURATION OF SEPARATION	SUBSTRATE	TISSUE FRACTION	O_2 UPTAKE IN 30 MIN.
Separation in distilled water			
hours			*cu. mm.*
1½	Succinate	Epithelium	110
		Stroma	21
	Phenylenediamine	Epithelium	125
		Stroma	5
Separation in physiologic saline			
2½	Phenylenediamine	Epithelium	92
		Stroma	112
2	Succinate	Epithelium	140
		Stroma	15
	Phenylenediamine	Epithelium	150
		Stroma	127
2½	Succinate	Epithelium	107
		Stroma	10
	Hydroquinone	Epithelium	101
		Stroma	60
Parallel samples			
1½*	Phenylenediamine	Epithelium	140
		Stroma	12
2½†	Phenylenediamine	Epithelium	160
		Stroma	75

* Separated in dist. water.

† Separated in physiol. saline.

activity, practically all of the activity is found in the epithelial fraction (Table III). This finding confirms our previous conclusions as to the location of the oxidase enzymes in this tissue.

When physiologic saline is used as the suspension fluid, it is found that considerable cytochrome oxidase can still be demonstrated in the stroma fraction when phenylenediamine or hydroquinone are used as substrates. These substrates are known to react directly with cytochrome c, and the oxygen uptake measured is evidence of cytochrome oxidase activity in that portion of the tissue which remains adherent to the stroma fraction on separation in saline but is removed on separation in distilled water. On the other hand, when succinate is used as the substrate no residual activity can be detected. This is particu-

TABLE IV

Oxygen Uptake in the Course of the Separation in Physiologic Saline

The amount of tissue used corresponds to 0.5 grams of the fresh unseparated tissue in each flask. Reagents added per flask: 0.7 cc. 1% cytochrome c, 25 mgm. succinate, 5 mgm. hydroquinone.

	O_2 UPTAKE IN 30 MIN.
	cu. mm.
Unseparated tissue	
Hydroquinone	143
Succinate	155
Stroma fraction with adherent epithelial residues after separation for 1 hour	
Hydroquinone	73
Succinate	38
Stroma fraction after separation for 2½ hours	
Hydroquinone	39
Succinate	0

larly well shown in the experiments summarized in Table IV in which as the separation of epithelium from stroma progresses, the rate of loss of succinate oxidizing capacity is much greater than the rate of loss of hydroquinone oxidizing capacity. It should be remembered that succinate is not directly oxidized by cytochrome c, but requires in addition the presence of succindehydrogenase, an enzyme generally found intimately associated with cytochrome oxidase in the same cell granule. Since the figures for the oxygen uptake which were obtained with some of the stroma fractions as source of the enzyme and with hydroquinone as substrate were rather small, an experiment was carried out in order to obtain data on the non-enzymatic oxidation of

hydroquinone under our experimental conditions. A separation was carried out for 3 hours and the residual stroma was ground. Stroma samples corresponding to one ciliary body were pipetted into four Warburg flasks. Two flasks were kept in a boiling water bath for 10 minutes after which they were cooled to room temperature. Phosphate buffer at a pH of 7.2 and hydroquinone were added to all four flasks and to one flask of each pair, cytochrome c. It can be seen (Table V) that the increase of the oxygen uptake due to addition of cytochrome c to the unheated samples, exceeds significantly the corresponding figure for the heated tissue. Only a small fraction of the oxygen uptake in the stroma after separation in physiologic saline is, therefore, due to autooxidation and the presence of a small but not negligible activity of cytochrome oxidase seems to be demonstrable.

TABLE V

Comparison of Heated and Unheated Stroma Fractions

Reagent added to each flask: 0.7 cc. 1% cytochrome c, 8.0 mgm. hydroquinone

	CYTOCHROME C	O_2 UPTAKE IN 30 MIN.
		CU. MM.
Unheated	+	52
	−	8
Heated	+	25
	−	12

The absence of succindehydrogenase might be attributed to the possibility that the dehydrogenase is more readily leached out of the tissue than the oxidase with which it is commonly associated. Using the cytochrome oxidase granules of heart muscle, Straub (7) has, in fact, been able to separate a fraction devoid of succindehydrogenase but this separation required an elaborate technique of mechanical grinding and repeated precipitation and resuspension. It is not to be supposed that simple stirring in physiologic saline solution would achieve a separation which had, until Straub, eluded the efforts of a great many biochemists. Furthermore, we find no cytochrome oxidase activity in the suspension fluid after centrifugation but only in the sediment. We are therefore forced to consider the possibility that the oxidase fraction remaining in the stroma portion that separation

in saline may actually be devoid of succindehydrogenase. Until very recently this possibility was counter to all experience, but Dounce (10) has reported the finding of cytochrome oxidase activity in the nucleus of liver cells unassociated with succindehydrogenase.

In regard to the ciliary body, experiments are being carried out in order to analyze this dissociation more quantitatively and over the whole course of the separation procedure. It is also planned to obtain more information about the alleged intermediators between succindehydrogenase and cytochrome oxidase and the histological relationship of these two enzyme systems.

SUMMARY

Methods are described for the isolation of the secretory portion of the ciliary body in beef eyes and for the stepwise removal of the epithelium from the stroma of this tissue. In support of conclusions reached from previous experiments, cytochrome oxidase activity of a high order has been found present in the epithelium, negligible in the stroma. A dissociation in the course of the separation of the rate of oxidation of succinate and hydroquinone has been observed in some tissue fractions. This phenomenon is now being studied in greater detail.

REFERENCES

1. J. S. Friedenwald and R. D. Stiehler, Arch. Ophth. **20:** 761, 1938.
—— and W. Buschke, Am. J. Ophth. **24:** 1105, 1941.
——, W. Buschke and H. Michel, Arch. Ophth. **29:** 535, 1943.
2. J. S. Friedenwald, H. Herrmann and R. Buka, Bull. Johns Hopkins Hosp. **70:** 1, 1942.
3. R. D. Stiehler and L. Flexner, J. Biol. Chem. **126:** 603, 1938.
4. D. Keilin and E. F. Hartree, Proc. Royal Soc. Biol. **122:** 298, 1937.
5. M. E. Krahl, et al., J. Gen. Physiol. **24:** 597, 1941.
6. E. Stotz, et al., J. Biol. Chem. **124:** 745, 1938.
7. D. Keilin and E. F. Hartree, Proc. Royal Soc. Biol. **125:** 171, 1938.
8. J. H. Quastel and H. M. Wheatley, Biochem. J. **32:** 936, 1938.
9. F. B. Straub, Z. physiol. Chem. **268:** 227, 1941.
10. A. L. Dounce, J. Biol. Chem. **147:** 685, 1943.

SALICYLATE THERAPY IN RHEUMATIC FEVER[1]

A Rational Technique

Lt. Comdr. ALVIN F. COBURN, (MC), U.S.N.R.[2]

The essential problem in the therapy of rheumatic fever is the prevention of disabling heart disease. If the rheumatic attack were always monocyclic, severe heart muscle damage would rarely occur. However, in children and young adults rheumatic fever is more commonly polycyclic and during each febrile phase of the cycle severe inflammatory reactions take place in vascular tissues. These reactions continue to occur so long as the respiratory pathogen (hemolytic streptococcus Group A) liberates antigen and induces an abnormal antibody response in the rheumatic subject (1). Since there are no methods available either for suppressing the elaboration of antigen by the bacterial agent or for modifying the constitutional defect of the host, effective handling of the rheumatic patient must depend, for the present at least, on a complete orchestration of all available therapeutic instruments. The objective in the treatment of each patient must be to reduce cardiac damage to a minimum, and to effect this it is essential that the inflammatory reaction of rheumatic fever be suppressed.

The only drug that has survived for half a century in the treatment of rheumatic fever is salicylate. And yet its use is still empirical and there is no consensus of opinion as to its value. Most clinicians agree that this drug has peculiar analgesic and antipyretic actions in rheumatic fever but few feel that salicylate modifies the progress of the disease process. There is no standard of dosage for the use of this drug and its administration to rheumatic children is frequently not advised. The reasons for this confusion in empirical salicylate therapy are apparent. Salicylate has no effect on the infectious agent and there is little evidence that the drug modifies the immune response of

[1] This study has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

[2] Present address: Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

the patient with rheumatic fever. Salicylate therapy therefore can not be expected to alter the potential duration of rheumatic activity. If, however, salicylate therapy modifies the sterile inflammatory reaction which occurs during activity of the rheumatic process, one may expect this effect to inhibit the development of cardiac disease. However, no such action has yet been clearly demonstrated. To determine whether salicylate can modify the rheumatic reaction, it is essential that the active drug component be identified, that its concentration in the blood stream be measurable and that the effect of various blood levels of active material on the inflammatory process be demonstrated. Since the rate of blood sedimentation in rheumatic fever is a reflection of the intensity of inflammation, one can use this index in conjunction with the clinical manifestations to evaluate the effect of salicylates on the rheumatic reaction. In the present paper the author has attempted first, to determine whether or not salicylate modifies the inflammatory reaction which characterizes activity of the rheumatic process, then to identify the active salicylate fraction and finally to develop a rational technique for the treatment of the rheumatic attack.

OBSERVATIONS ON THE MODE OF ACTION OF SALICYLIC ACID

The mode of action of salicylate in rheumatic fever is unknown. However, two types of studies have indicated that the salicyl radicle has peculiar activity in vivo and in vitro. Lutwak-Mann (2) has made an exhaustive study of the effect of salicylate on enzymes and metabolic processes. Although salicylic acid in physiological concentrations has little effect on the known enzyme systems, it exerts profound changes in metabolism. Soon after salicylate is injected into the experimental animal "there is a disappearance of nearly all liver glycogen and its full restoration 24 hours later clearly indicates an effect on several as yet unidentified enzymic processes." Furthermore Lutwak-Mann has shown that in B_1 deficient rats the oxidation of dihydroxyacetone by liver slices is diminished by salicylate. The specificity of salicylate is shown by an increase in the reducing power of the urine, which effect is not produced by salicylic aldehyde until the latter is transformed into salicylic acid.

Immunological studies (3) have shown that sodium salicylate pre-

vents the precipitation of antigen by antibody in vitro; that this effect is more marked as the concentration of salicylate in the system is increased; that the immune system becomes progressively less sensitive to the action of salicylate as the excess of antibody becomes larger (more salicylate being required to offset antibody excess); that the effect of salicylate is more marked than is observed in other anions of the lyotropic series and that the effect appears to be due to its action on antibody. Whether salicylate exerts a similar effect in vivo is not known. However, even if salicylate does modify immune reactions in vivo, the final effect may, nevertheless, be exerted on a cellular enzyme system. It does not appear that such an effect occurs on the known systems. Further fundamental work on the isolation of enzymes not yet recognized will be required before this promising approach can be expected to yield positive results.

OBSERVATIONS ON THE METABOLISM OF SODIUM SALICYLATE BY THE HUMAN SUBJECT

It has recently been shown (4) that the human host metabolizes salicylate with the excretion of at least four fractions. Normal adolescents and adults excrete about four-fifths of ingested salicylate in forms containing intact salicyl groups; about 20 per cent of the excreted salicyl is in unchanged salicylate; about 53 per cent is in salicylurate and about 25 per cent in glucuronides. About 4–8 per cent of the ingested salicyl is converted to gentisic acid and related compounds. Patients with acute rheumatism excrete a smaller proportion of the unchanged salicylic acid than normals, a fact previously pointed out by Hanzlik *et al.* (5). This low level of excretion of salicylic acid in rheumatic fever is apparently due to more extensive modification of salicyl in the body rather than to storage, as the deficits are not made up later in the course of medication or after medication is stopped, and salicyl in sweat and feces was found by Hanzlik to be negligible. Furthermore, patients who give a good clinical response to salicylate and whose temperatures fall rapidly to normal show low outputs of salicylic acid for only a few days, and after the remission of fever has occurred the amounts of salicyl excreted are within normal range. Rheumatic fever patients excrete relatively large amounts of salicyl in conjugated form, approximately two to four times as high as with normal subjects.

It is also of interest that the rheumatic patients who show the best clinical response including the patients who receive salicylate intravenously excrete a larger proportion of the drug in the form of salicyl than patients who have not responded satisfactorily. These findings suggest that some of the salicylic acid reacts with the inflammatory process and is thereby conjugated. The combined evidence is compatible with the possibility that the salicylate effect in rheumatic fever is dependent on the concentration of the circulating salicyl radicle.

PRELIMINARY OBSERVATIONS

A preliminary study on the effect of sodium salicylate in rheumatic fever was made on a group of sixty-four patients whose clinical manifestations have been reported (6). These individuals, with ages ranging from 17 to 28, were admitted to the hospital early in an acute attack of rheumatic fever. With few exceptions all were free of detectable signs of heart disease. Two modes of salicylate therapy were instituted and the effect of small and large doses on the clinical course and blood sedimentation rate was observed. The incidence of persistent heart lesions to be expected in this group was not known. It is of interest, however, that in a recent study, Green (7) observed that of 114 cases of rheumatic fever in the Royal Navy, 1 died, 49 developed serious heart disease and 31 were stigmatized with a persistent systolic, mitral murmur.

Group 1 consisted of 43 cases who received sodium salicylate only for the relief of symptoms and pyrexia. The daily regime ranged from intermittent doses to 3 to 6 grams. Twenty-four of these patients had mild monocyclic attacks; their blood sedimentation rates returned to normal levels in two to four weeks; none developed signs of progressive heart disease. Nineteen patients had polycyclic attacks; their blood sedimentation rates fluctuated and remained elevated from four to twenty weeks with an average of nine weeks. Sixteen of these patients developed mitral valvular disease, and in five of the sixteen, signs of aortic insufficiency became manifest while they were bed patients. In summary, about 40% of this group treated symptomatically with sodium salicylate had polycyclic rheumatic attacks and all but three developed cardiac valvular disease. One patient of this group manifested a fulminating attack while being treated symptomatically with salicylate. His case history is as follows:

Case #1. This 19 year old patient was admitted with a severe rheumatic attack accompanied by pulmonary solidification. With oral doses of sodium salicylate, 10 grams daily, improvement was rapid. The drug dosage was lowered after one week to 2 grams daily and the patient remained asymptomatic for a few days. He then suddenly developed pericarditis, hyperpyrexia, nausea, severe abdominal pain, heart block and pulmonary solidification. For weeks his condition was critical. He recovered after an illness of more than 9 months but remained stigmatized with advanced heart disease.

Group 2 consisted of seven patients with severe attacks who were treated with 10 grams of sodium salicylate daily until their sedimentation rates remained normal for two weeks. In contrast to the sixteen patients discussed above all of these seven individuals showed a progressive fall in the blood sedimentation rates. Normal levels were reached between the fifteenth and thirtieth day. None developed signs of valvular heart disease.

TABLE I

The Blood Sedimentation Rates, mm. in one hour, of Twelve Rheumatic Fever Patients Receiving Intravenous Salicylate

DAY OF R.	1	2	3	4	5	6	7	8	9*	10	11	12*
0		17	106	117	52	115	70	90	110	105	85	110
2	60	90	95	119				90	113	107		115
4	40		70	113			80	80	125	111		124
6	30		64	100	33	129	57	67	95	86		
8	25	52	59	81			55		70	75	60	90
10		37	57	60		100	47		70	64		
12	25		28	25			31	45	56	50		76
14	20	28	20		19	55	24	30		42	9	55

* Patient #12 had the most intense polyarthritis encountered in this study. Continuous infusions of 20 grams of sodium salicylate daily for three days were required. See case #2 below.

Patient #9 had intense purpura in addition to severe polyarthritis and carditis. Both of these patients were placed on oral doses and the sedimentation rates fell progressively to normal.

Group 3 consisted of twelve patients with severe rheumatic attacks. Each received daily infusions of 10 grams of sodium salicylate for two weeks. The changes in the sedimentation rates during intravenous therapy are shown in Table I. And figure A illustrates the relation

of these changes to the administration of salicylate in patients #5 and #6 of Table I.

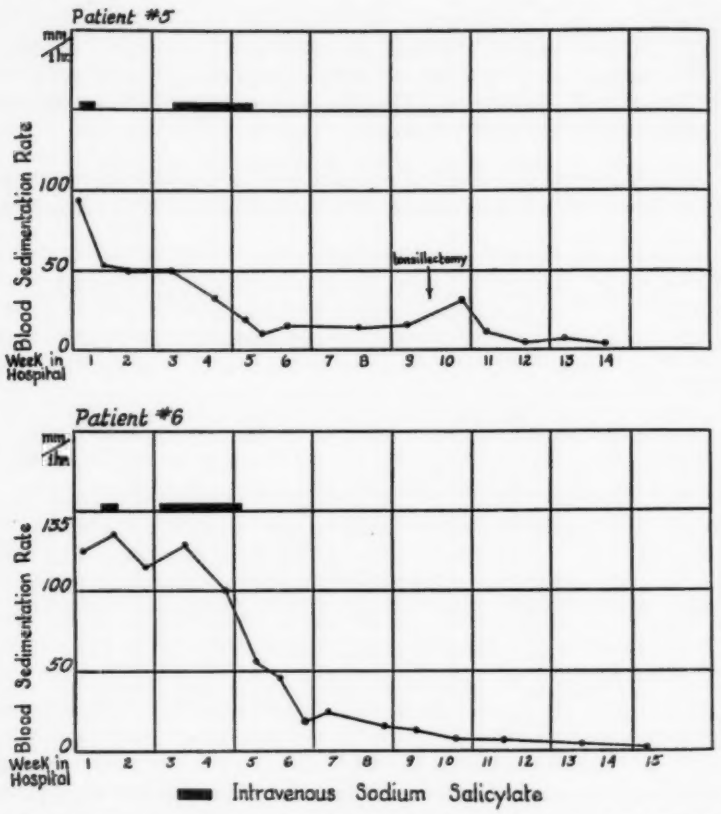


FIG. A. These curves show that the blood sedimentation rates fell following the intravenous administration of sodium salicylate.

Without exception these sedimentation rates fell progressively and were normal or approaching normal after fourteen infusions. At this time sodium salicylate in doses of 10 grams daily was administered orally until the sedimentation rates remained normal for two weeks. These patients escaped valvular heart disease. One exceptional case

required 20 grams daily for the first 72 hours early in the attack. His case history is as follows:

Case #2. This 40 year old patient was admitted with a respiratory infection. Following this he had a febrile episode which was treated with sulfonamide for ten days. At the end of this period he developed an extremely severe polyarthritis and fever. Oral doses of sodium salicylate, 10 grams daily for three days, were administered without effect. An infusion of 10 grams of sodium salicylate was also ineffective. The patient was then placed on a continuous infusion of sodium salicylate for three days. After receiving 20 grams he began to have relief from pain and after 60 grams he was symptom-free. A daily infusion of 10 grams was given for nine days and this was supplemented with oral doses of 10 grams daily. Recovery was progressive. He escaped clinical signs of heart involvement.

There were three additional patients whose clinical response to oral daily doses of 10 grams was not satisfactory. These men recovered promptly following daily infusions of 10 grams of sodium salicylate. At that time methods for blood level determinations were not available and it is not known whether these individuals failed to absorb sodium salicylate or whether they metabolized the drug abnormally. An illustrative case is as follows:

Case #3. This 21 year old patient was admitted on the first day of a rheumatic attack. He was given sodium salicylate orally without relief of symptoms. On the eleventh day when his temperature was 103 degrees he was given an infusion of 10 grams and within two hours became asymptomatic and was afebrile 24 hours later. Infusions were continued for ten days. Recovery was rapid and progressive. He escaped clinical signs of heart disease.

In summary, this preliminary study indicated that about 40% of 43 young adults treated symptomatically with sodium salicylate manifested rheumatic activity for more than one month and showed a marked tendency to develop valvular heart disease and that all 18 patients treated with daily doses of 10 grams or more of sodium salicylate either orally or intravenously showed rapid clinical recovery and a progressive fall in the blood sedimentation rate. Although half of the eighteen patients had electrocardiographic evidence of carditis on admission, none developed clinical signs of valvular heart disease. These preliminary studies suggested that doses of 3 to 6 grams were adequate for the relief of pain and pyrexia but failed to suppress the inflammatory reaction, that doses of 10 grams not only brought symp-

tomatic relief but also modified the rheumatic reaction and that both effects were obtained most rapidly in patients receiving sodium salicylate intravenously, and that in exceptionally severe attacks larger intravenous doses were required at the onset. None of these patients developed evidence of renal irritation and prothrombin determinations were normal in the six individuals tested.

FURTHER OBSERVATIONS

The urinary studies already referred to suggested that the salicyl radicle modifies the rheumatic reaction. However, proof of this depended on the development of a method of determining salicylate blood levels. Recently, a satisfactory method has been developed for measuring the concentration of the salicyl radicle in plasma (8). So far as can be determined this method is specific for free salicyl. In the present study it was adopted as a routine laboratory procedure.

METHOD FOR DETERMINING THE PLASMA LEVEL OF SALICYLIC ACID

One cc. of plasma is placed in a 30 cc. stoppered flask. To this is added 0.5 cc. 5 N HCl and 20 cc. of ethylene dichloride. The flask is agitated on a shaking machine for at least 5 minutes. An aliquot of 10 cc. is removed in a syringe with a long needle, special care being taken not to contaminate the ethylene dichloride layer with the supernatant acid water layer. The ethylene dichloride aliquot of 10 cc. is placed in another stoppered flask to which is added 10 cc. of distilled water and 0.5 cc. of 1% ferric nitrate. The flask is again agitated in the shaking machine for five minutes. About 7 cc. of the supernatant, purple water layer are removed. The color is matched promptly in a colorimeter against a known standard concentration of sodium salicylate in plasma which was treated in parallel with the samples to be tested. The content of salicylate in the plasma is calculated. It is convenient to use larger quantities of plasma if the salicyl radicle is below 100 gamma per cc. The content of drug in the erythrocytes is negligible.

PERSONNEL STUDIED

Fifty-eight patients with attacks of rheumatic fever were studied in the spring of 1943 to determine the relation of plasma salicylate levels

to the effectiveness of salicylate therapy. Those patients were similar to the group used in the preliminary studies of 1942. They were males between the ages of 17 and 30; many of them manifested carditis on admission and most of them had severe attacks. The general care administered to these patients was the same given to the group in the preliminary study (6). Each patient was observed for one day prior to the institution of therapy so that clinical appraisal and indicated laboratory tests might be completed. The changes in blood sedimentation rates were determined on the rheumatic fever ward at frequent intervals by the Westergren method and plasma salicylate tests were done in the laboratory of the Norfolk Naval Hospital. All patients were treated in an identical manner except for the dose of sodium salicylate administered.

TABLE II

Plasma Salicylate Levels in Relation to Dosage Administered Orally Every Four Hours

	DAILY DOSE						
	2.6 gms.	4 gms.	5.3 gms.	6 gms.	6.6 gms.	8 gms.	10 gms.
High level	88	227	263	234	288	285	454
Low level	40	134	150	170	156	267	326
Mean level	62	164	179	190	210	276	356

PLASMA SALICYLIC ACID LEVELS IN RHEUMATIC PATIENTS

Variations in Plasma Levels with Dosage. The plasma levels for seven different oral doses were determined on thirty patients. Repeated tests were made on the same patients at intervals of a few hours or several days. After the patient had been on a dose for three days there was little fluctuation in plasma level. The plasma levels in men weighing between 120 and 170 pounds are presented in Table II. Throughout this study all values are expressed as gamma per cc. plasma.

Rise in Plasma Levels with Increasing Doses. Two types of observations were made. One group of patients who had received no sodium salicylate was given 1.6 grams every four hours day and night. Determinations were made before and for several days after the administration of 10 grams daily. The changes in plasma levels are shown in Table III.

It is seen in Table III that peak levels were attained after the ingestion of 20 grams of drug and maintained while this dosage of 10 grams daily was continued.

A second group of patients who had been maintained on small amounts of sodium salicylate had their doses increased to 1.6 grams every four hours day and night. Peak plasma levels were reached in 24 or 48 hours after receiving 10 grams. Illustrative examples showing the rises in plasma levels are presented in Table IV.

TABLE III

The Rise in Plasma Salicylate Levels of Ten Patients Receiving Sodium Salicylate, 10 gms. Daily, by Mouth

DAY OF R	TOTAL ORAL DOSAGE	1	2	3	4	5	6	7	8	9	10
	gms.										
0	0	0	0	0	0	0	0	0	0	0	0
1	3.3	208	202	163	198	153	163	242	163	240	227
2	13.3	250	308	290	312	234	312	353	312	329	441
3	23.3	416	335	357	405	326	326	405	312	357	—
4	33.3	384	263	388	312	272	357	353	—	523	349

TABLE IV

The Rise in Plasma Salicylate Levels after Increasing the Oral Dose to 10 Grams Daily

	ORAL DOSAGE				
	2.6 gms.	5.3 gms.	6 gms.	6.6 gms.	8 gms.
Plasma level	40	220	138	156	267
Plasma level 24 hrs. after 10 gms.	326	375	250	341	326
Plasma levels 40 hrs. after 10 gms.	469	375	341	300	336

Fall in Plasma Levels on Discontinuing Therapy. Stopping of drug therapy was followed by a rapid fall in plasma level within 24 hours. With one exception no salicylate was detected in 2 cc. of plasma 48 hours after the last dose. The fall in plasma levels following the withdrawal of drug is shown in Table V.

Relation of Plasma Levels to Body Weight. Fifty patients were maintained on daily oral doses of 10 grams. Several plasma level determinations were made on each patient and the average recorded in this

table. The relation of the plasma levels to salicylate dosage per kilogram body weight is shown in Table VI.

It is seen in Table VI that the maximum value on this dosage was 454, the minimum 215, the mean 368 and the median 375. Patients receiving only 100 or 110 mgm. per kg. body weight had low plasma levels. With doses varying between 130 and 190 mgm. of drug per kg. of body weight the plasma levels varied between 312 and 454 irrespective of body weight.

A Comparison of Plasma Level Rises in Patients Receiving Sodium Salicylate Orally and Intravenously. Five patients were given 4 grams of sodium salicylate by mouth and plasma level determinations made

TABLE V

The Fall in Plasma Salicylate Levels on Withdrawal of Salicylate Therapy

CASE	PLASMA LEVEL ON 10 GMS. DAILY	24 HRS. AFTER LAST DOSE	48 HRS. AFTER LAST DOSE
1	405	300	133
2	312	100	0
3	272	100	0
4	312	107	0
5	351	100	0
6	384	198	0
7	384	234	0
8	313	93	0
9	395	242	0
10	330	107	0

1, 5, 9 and 24 hours later. Peak levels were reached in each case at the end of 5 hours. Three days later the same patients were given 4 grams intravenously. Peak levels were reached at the end of the infusions and as is shown in Table VII were similar.

It has been stated above that patients receiving salicylates every four hours by mouth did not reach peak plasma levels until 48 hours after drug therapy was instituted. The rise to peak levels during the first 48 hours of treatment is shown in Table VIII.

In contrast to individuals on oral doses patients receiving 10 grams intravenously reached peak plasma levels at the end of the infusion. Following the conclusion of treatment there was a steady fall in the plasma salicylate level. These changes are shown in Table IX.

TABLE VI

Plasma Salicylate Level in Relation to Dosage per Kilogram of Body Weight

CASE NUMBER	GRAM OF SODIUM SALICYLATE PER KG. BODY WEIGHT	PLASMA SALICYLIC ACID
		gammas per cc.
1	.19	336
2	.19	375
3	.17	384
4	.17	350
5	.17	375
6	.17	405
7	.17	423
8	.17	341
9	.17	395
10	.16	416
11	.16	312
12	.16	416
13	.16	312
14	.16	335
15	.15	375
16	.15	316
17	.15	313
18	.15	326
19	.15	371
20	.15	357
21	.14	441
22	.14	431
23	.14	353
24	.14	411
25	.14	441
26	.14	365
27	.14	454
28	.14	475
29	.14	371
30	.13	326
31	.13	354
32	.13	441
33	.13	385
34	.13	415
35	.13	428
36	.13	330
37	.13	430

TABLE VI—*Continued*

CASE NUMBER	GRAM OF SODIUM SALICYLATE PER KG. BODY WEIGHT	PLASMA SALICYLIC ACID
		gammas per cc.
38	.13	312
39	.13	375
40	.13	357
41	.13	421
42	.11	306
43	.10	227
44	.10	215

TABLE VII

Maximum Levels of Plasma Salicyl in Patients Receiving Two Types of Therapy—Dose, 4 Grams

CASE	FIVE HRS. AFTER ORAL DOSE	AT END OF INFUSION
1	261	264
2	229	244
3	236	304
4	273	277
5	266	238

TABLE VIII

The Rise in Plasma Salicylate Levels During the Ingestion of 20 grams of Sodium Salicylate

TIME	TOTAL DOSAGE	CASE #1	CASE #2
hrs.	*grams*		
6	3.3	156	120
8	5	208	—
24	10	250	240
48	20	416	329

TABLE IX

Changes in Plasma Salicylate Levels Following the Intravenous Administration of 10 grams

	CASE #1	CASE #2	CASE #3
Before infusion	0	0	0
At end of infusion of 10 gms.	550	332	395
2 hrs. later	454	234	375
4 hrs. later	259	267	300
7 hrs. later	259	214	278
24 hrs. later	190	178	169

Patients who received daily infusions of 10 gms. of sodium salicylate showed a tendency to build up a plasma level in some instances but not in others. The plasma levels 20 hours after infusion are shown in Table X.

It has been shown above that the oral administration of 10 grams of sodium salicylate daily will provide an average plasma level of 368 gamma. Increasing this oral dosage frequently leads to gastric irritation, nausea and vomiting. However, several patients in this series

TABLE X

Changes in Plasma Salicylate Levels Following Repeated Infusions Showing Values 20 hours after Infusion

NO.	CASE #1	CASE #2	CASE #3	CASE #4	CASE #5
INFUSION 1	150	187	234	225	278
2	250	357	312	428	268
3	500	340	340	192	287
4	395		250	135	294
5	407			100	
6				50	

TABLE XI

Changes in Plasma Salicylate Levels During and Following Infusions of 20 Grams of Sodium Salicylate

	CASE #1	CASE #2
Before infusion	268	428
After 10 gms.	465	500
After 15 gms.	476	555
After 20 gms.	605	666
5 hrs. later	500	—

were given 20 grams in 8 hours by vein without untoward effects. The plasma levels reached during these infusions are shown in Table XI.

The intravenous administration of sodium salicylate made it possible to reach plasma levels of over 600 gamma per cc. The only symptom observed by patients who received about 2.5 grams per hour was mild tinnitus.

In summary, the salicylate plasma content is readily brought up to 400 gamma per cc. in four hours by intravenous administration;

whereas it takes two days to develop this level with oral doses. The plasma level remains fairly constant after the second day of sodium salicylate oral therapy. However, following intravenous therapy the level shows a marked drop 12 hours later. Attaining plasma levels of over 600 gamma per cc. is difficult or impracticable with oral doses but is possible when 20 grams are given intravenously during a period of eight hours.

THE RELATION BETWEEN PLASMA SALICYLATE LEVELS AND THE BLOOD SEDIMENTATION RATES

It is difficult to determine whether any form of treatment has a therapeutic effect in rheumatic fever because about 20% of young adults may be expected to have monocyclic attacks and recover spontaneously in about three weeks with symptomatic treatment. To determine whether the salicylate blood level influences the blood sedimentation rate the author selected 40 out of 58 patients on the rheumatic fever ward. Observations were confined to twenty patients with proven polycyclic attacks and to twenty other patients with attacks so severe that it seemed unlikely that they would be monocyclic. Observations were made to determine whether there was an association between the plasma salicylate concentration of these forty patients and the blood sedimentation rate.

Group 1. Twenty patients with prolonged rheumatic activity were selected for determining whether there is an association between the rheumatic reaction as reflected by the blood sedimentation rate and clinical symptoms. Four had active and severe carditis; the others had polyarthritis but were free of pain on daily doses of 6 grams or less of sodium salicylate. The blood sedimentation rates of each of these patients fluctuated; none fell progressively; all were elevated at the time of testing and had been elevated in the hospital ward for an average of 49 days. The plasma salicylate levels varied from 0 to about 250 gamma per cc.

Following the institution of daily oral doses of 10 grams of sodium salicylate the plasma levels rose in 48 hours to a range between 331 and 454 with an average maintenance level of 368 gamma per cc. At this plasma level the sedimentation rates of each patient fell within six days and continued to fall progressively to normal so long as this

plasma level was maintained. All of the sedimentation rates became normal in fourteen days or less. Curves showing the fall in blood sedimentation rates with rise in plasma salicylate levels are shown in figures 1 and 2. Two illustrative cases are recorded briefly.

Case #4. This 18 year old patient was admitted with a complaint of pains in his knees. For two months he was kept at bed rest without salicylate therapy. During this time he had a polycyclic course with fever between 99 and 103, with

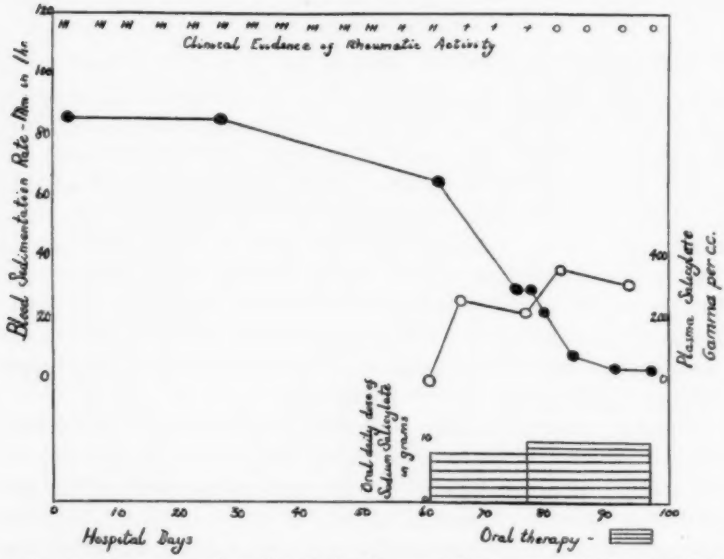

Clinical Evidence of Rheumatic Activity
Blood Sedimentation Rate - Mm in 1 hr
Plasma Salicylate Gamma per cc.
Oral daily dose of Sodium Salicylate in grams
Hospital Days
Oral therapy

FIG. 1. These curves show the relation in case #4 between the fall in the blood sedimentation rate and the rise in plasma salicylate level with increasing dosage of sodium salicylate.

vague aches and E. K. G. changes of first degree heart block, shifting pacemakers and premature ventricular contractions. Six weeks after admission, mitral systolic and aortic diastolic murmurs became audible.

After two months hospitalization he was given 6 grams of sodium salicylate and two weeks later this was increased to 10 grams. The blood sedimentation rate which had remained elevated became normal and there was rapid and progressive clinical improvement. The patient is stigmatized with aortic insufficiency and mitral stenosis. See Figure 1.

Case #5. This 18 year old patient was admitted at the onset of his first attack of rheumatic fever with the complaint of painful joints. He was treated with sodium salicylate, 5 grams for 6 days and became symptom-free. For two months he experienced polycyclic rheumatic fever with pyrexia and a markedly elevated blood sedimentation rate and developed a systolic mitral murmur. Infusions of sodium salicylate 10 grams daily were administered with a striking effect on the blood sedimentation rate. Pallor disappeared; he gained 10 pounds in weight; vague aches and weakness disappeared. After one month's treatment he was restored to good health and the cardiac findings were normal. See Figure 2.

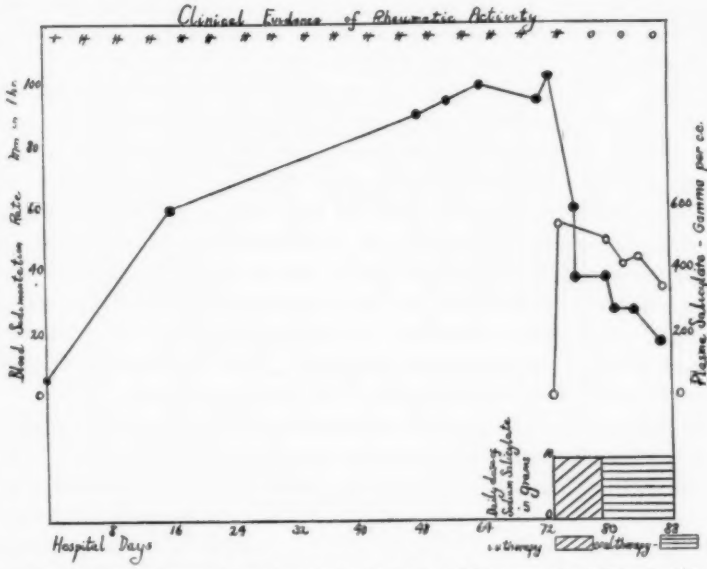


FIG. 2. These curves show the relation in case #5 between the fall in the blood sedimentation rate and the rise in plasma salicylate content with two types of salicylate therapy.

The induction of a high plasma salicylate level was followed not only by a rapid progressive fall in the blood sedimentation rate but also by a marked and rapid improvement in the clinical appearance. Pallor disappeared; appetite improved; there was a marked gain in weight in several patients; many noted that they slept soundly for the first time in many weeks. In summary, it seemed that although these patients were symptom-free while taking small doses or no salicy-

late they, nevertheless, manifested signs of a continuing inflammatory process. Furthermore it appeared that with the elevation of the plasma levels to about 368 gamma per cc. all evidences of inflammation disappeared promptly.

Group 2. These fourteen patients were treated daily with 10 grams of sodium salicylate by mouth during the first cycle of a severe rheumatic attack. All became symptom-free between 24 and 48 hours and afebrile in 72 hours. In several instances the blood sedimentation rate rose in the first five days of treatment. Following this the rate fell progressively to normal in each case. Except for one patient with intractable pustular acne all had normal sedimentation rates in 9 to 21 days. The average time required for the sedimentation rate to return to normal with a plasma salicylate level of over 368 gamma per cc. was 17 days. The sedimentation rates of these patients before treatment varied between 52 mm. and 103 mm. with an average of 86 mm. After the plasma salicylate level reached the range of 300 to 400 gamma per cc. all evidences of carditis disappeared and all of these patients escaped clinical signs of valvular heart disease. It appeared that the inflammatory reaction was suppressed when the plasma salicylate levels were maintained at 368 gamma per cc. and that the development of valvulitis was prevented. The blood sedimentation rate curves of these fourteen patients are shown in figure 3.

Group 3. It has been stated above that the plasma salicylate level reaches the 300 to 400 gamma range after two or three days of oral doses of 10 grams daily. It has also been shown that this level can be reached in four hours when the drug is administered intravenously and that levels of 500 to 650 gamma can be produced by intravenous medication without causing disturbing symptoms. To test the effect of raising the plasma level rapidly and avoiding a lag of forty-eight hours six patients were given daily infusions of 10 grams of sodium salicylate. These were all severely ill patients with blood sedimentation rates averaging 94 mm. in one hour. The results of this form of therapy were observed closely during the infusions. Patients became symptom-free in four hours, afebrile in 24 hours and the sedimentation rates of all six cases became normal within two weeks. The average time required was ten days. This is shown in figure 4.

Curves showing the relation between drug dosage, plasma levels,

fall in blood sedimentation rates and disappearance of clinical symptoms are shown in figure 5. An illustrative case history is recorded briefly.

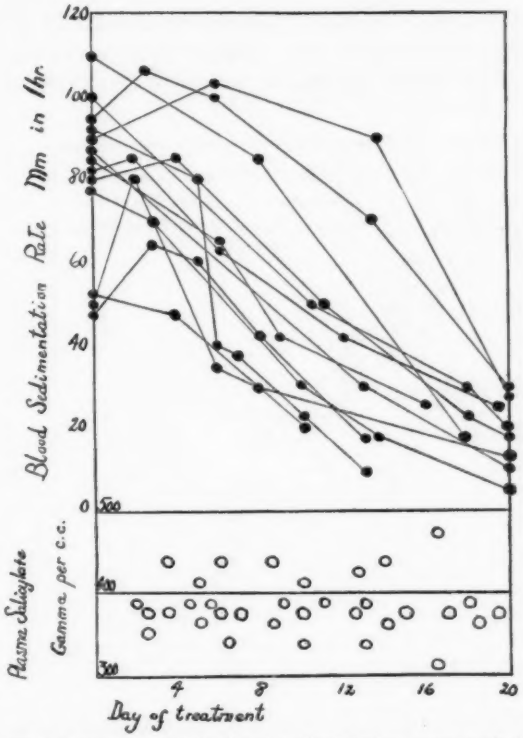


FIG. 3. This shows the fall in blood sedimentation rates and the distribution of plasma salicylate levels during oral salicylate therapy, 10 grams daily.

Case #6. This 24 year old patient was admitted on the tenth day of a severe rheumatic attack. He was unable to turn in bed because of an intense polyarthritis. The oral temperature was over 103 degrees and the electrocardiogram showed first degree heart block. During the first infusion of sodium salicylate, 10 grams he experienced great relief from pains and within 24 hours became afebrile and asymptomatic. The heart block (E. K. G.) disappeared promptly and recovery was progressive. He escaped clinical signs of heart disease.

It was observed that all symptoms subsided in these six patients before the initial infusion was completed. In four instances the temperature fell to 98 degrees and remained normal. In two the mouth temperature fell to a range between 99 and 100 degrees but did not reach normal within 24 hours. In these two patients 20 grams were administered on a subsequent day. With these large doses given over a period of eight hours the plasma salicylate level rose above 600

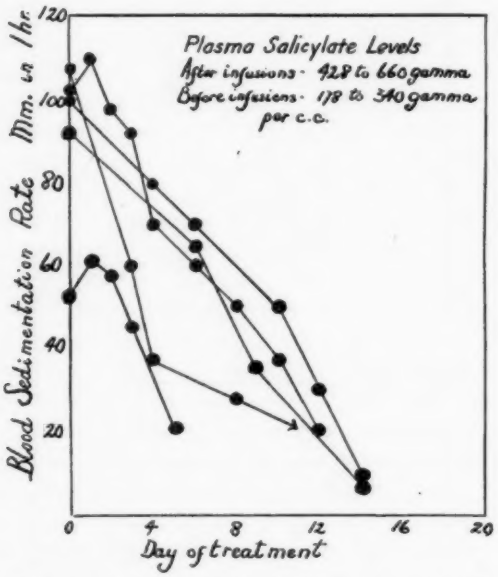


FIG. 4. This shows the fall in the blood sedimentation rate following infusions of sodium salicylate, 10 grams daily.

gamma per cc.; the temperature fell to 98 degrees and remained normal thereafter on doses of 10 grams daily. It is of interest that the two patients requiring these high plasma levels were the sickest, with sedimentation rates of 97 mm. and 115 mm. The relation between therapy and its effect on clinical symptoms, plasma salicylate level of salicylic acid and the blood sedimentation rate is shown in figure 6 and 7. Two case histories are recorded briefly.

Case #7. This 20 year old patient was admitted during the second week of a moderately severe polyarthritis with an oral temperature of 102 degrees. Following 10 grams of sodium salicylate intravenously he experienced some relief of symptoms but did not become completely asymptomatic and afebrile until an infusion containing 20 grams of sodium salicylate was administered. Following this

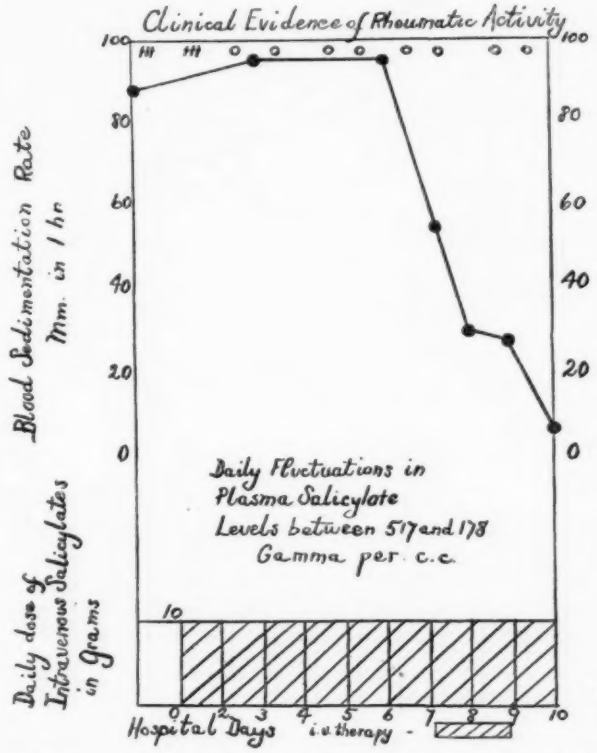


FIG. 5. This shows the fall in blood sedimentation rate of case #6 receiving 10 grams of sodium salicylate daily by vein.

recovery was rapid and progressive and the patient escaped clinical signs of heart disease. See Figure 6.

Case #8. This 26 year old patient was admitted during the first week of a severe rheumatic attack, with intense polyarthritis. The oral temperature was 102 degrees and the heart overactive. An infusion of 20 grams of sodium salicylate

was administered with relief of all pain during the infusion. The temperature and pulse became normal within thirty-six hours. Recovery was rapid and progressive. The patient escaped clinical signs of heart disease. See Figure 7.

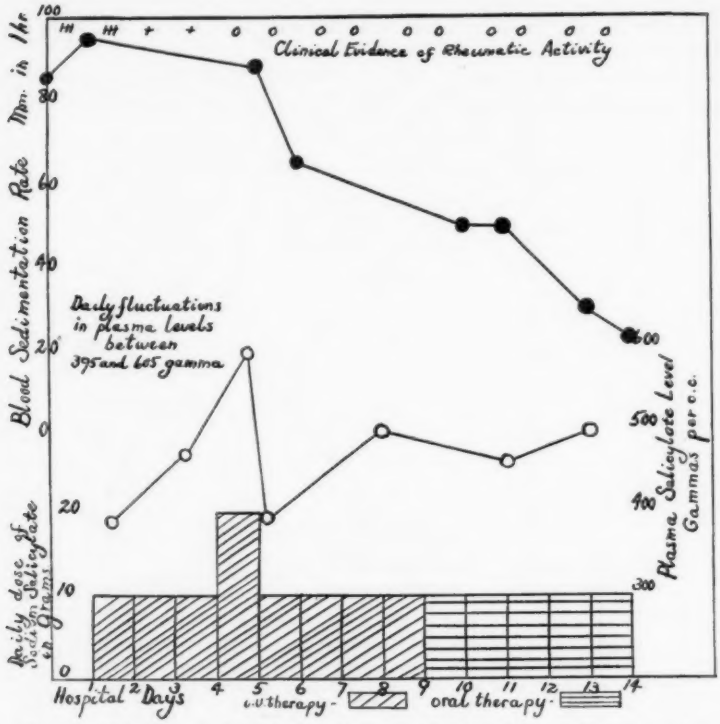

Clinical Evidence of Rheumatic Activity
Blood Sedimentation Rate Mm. in 1 hr
Daily fluctuations in plasma levels between 395 and 605 gamma
Plasma Salicylate Level Gammas per c.c.
Daily dose of Sodium Salicylate in Grams
Hospital Days
i.v. therapy
oral therapy

FIG. 6. This shows the relation between blood sedimentation rate, plasma salicylate level and drug dosage in case #7.

In summary, the intravenous administration of sodium salicylate makes it possible to build up a plasma salicylate level of 400 or if necessary 650 gamma per cc. in a few hours and without causing symptoms other than mild tinnitus. At this range of blood values the symptoms disappeared at once; the temperature reached normal promptly; the elevated blood sedimentation rate fell within a few days, declined progressively to within normal limits which were reached between one and two weeks.

Group 4. The conductor of a therapeutic experiment finds it difficult to differentiate between spontaneous recovery and drug effect. If one tests out the withdrawal of salicylates early in an attack of acute rheumatism, symptoms of pyrexia return within 48 hours unless the patient is making a spontaneous recovery. However, such an exacer-

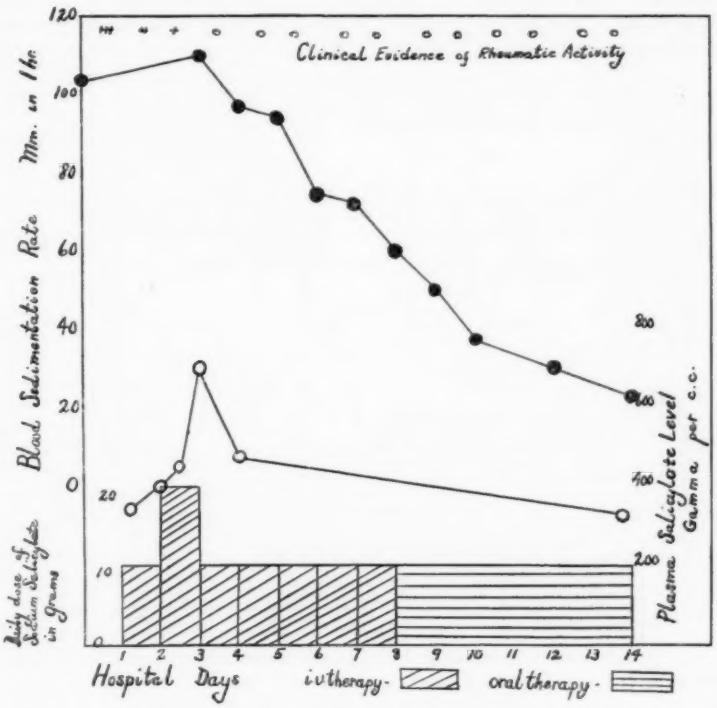

Clinical Evidence of Rheumatic Activity
Blood Sedimentation Rate Mm. in 1 Hr.
Daily dose of Sodium Salicylate in grams
Plasma Salicylate Level Gamma per c.c.
Hospital Days
i.v. therapy
oral therapy

FIG. 7. This shows the relation between blood sedimentation rate, plasma salicylate level and drug dosage in case #8.

bation of symptoms may endanger the patient's life as was shown above (case #1, page 439). Since one patient in this group developed severe symptoms of salicylism it was necessary to withdraw salicylates. The relations between the administration and withdrawal of drug to the clinical and laboratory findings are shown in figure 8, and the case history is presented.

Case #9. This 19 year old patient was admitted on the fourth day of a severe attack of rheumatic fever characterized by polyarthritis, fever above 102 degrees and pulse of 130. He was given an infusion of 20 grams of sodium salicylate. All symptoms disappeared during the infusion; the temperature became normal within twelve hours and the tachycardia disappeared twenty-four hours later. Recovery was rapid and progressive. The patient became restless on the tenth day. The temperature rose to 101 and then mental confusion followed. Drug therapy was discontinued. The patient developed a severe psychosis, fluctuating between periods of coma and manic excitement. The spinal fluid was normal. Fluids

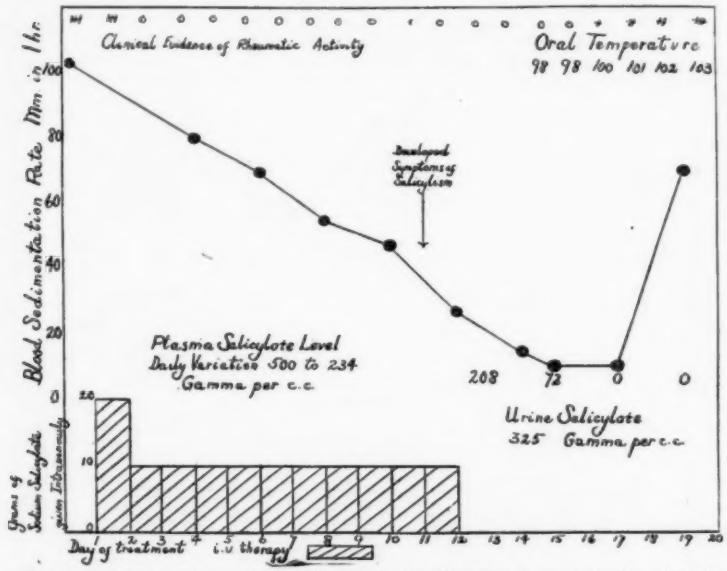


FIG. 8. This shows the relation of the blood sedimentation rate to the administration and withdrawal of salicylate therapy in case #9.

were forced for two days by intravenous infusions. By the third day salicylate disappeared from the plasma but was still excreted in high concentration in the urine. Recovery was rapid and complete.

Two days later the patient had a severe exacerbation of rheumatic manifestations. An attempt to administer small oral doses of sodium salicylate was followed by the appearance of a generalized maculo-papular rash and mental confusion which promptly disappeared when the drug was discontinued. This was the only patient encountered in this study who developed untoward symptoms from salicylate. He was kept under observation for three months, at the end of which

his symptoms subsided and the blood sedimentation rate returned to normal. He was then transferred for convalescent care.

Two patients whose sedimentation rates had been normal for more than two weeks developed a rheumatic exacerbation shortly after the

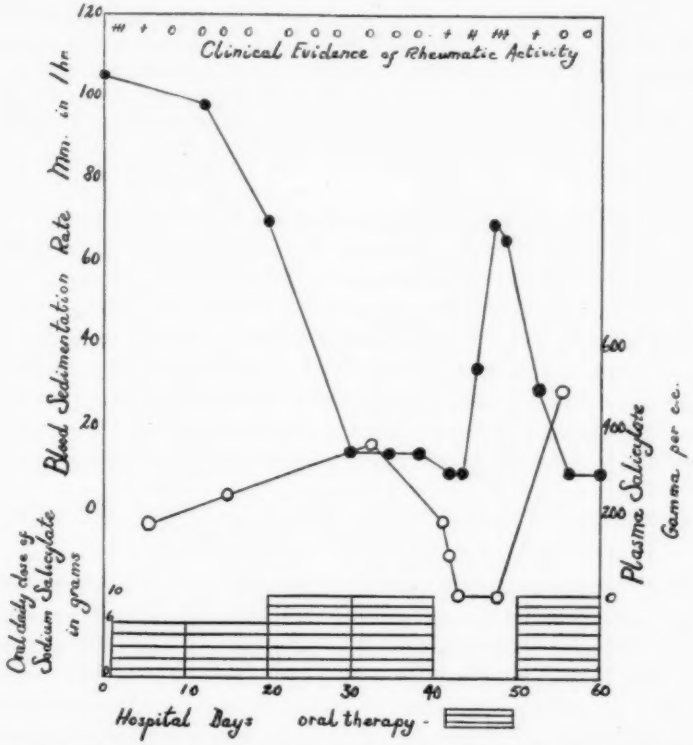

Clinical Evidence of Rheumatic Activity
Blood Sedimentation Rate Mm. in 1 hr.
Plasma Salicylate Gamma per c.c.
Oral daily dose of Sodium Salicylate in grams
Hospital Days
oral therapy

FIG. 9. This shows the relation of clinical symptoms, blood sedimentation rate and plasma salicylate level to salicylate therapy during an acute attack and an exacerbation of rheumatic fever in case #10.

institution of a trial week without sodium salicylate. The clinical response to the resumption of therapy, which could not be tested in the previous case, was prompt in both cases. Figure 9 shows the relation of the institution, withdrawal and resumption of salicylate therapy

to the clinical picture and blood sedimentation rate. One case history is presented briefly.

Case #10. This 24 year old patient was admitted during the second week of a severe rheumatic attack characterized by intense polyarthritis and first degree heart block. During the first three weeks he received 6 grams of salicylate daily with symptomatic relief but with little effect on the blood sedimentation rate and heart block. A course of salicylate, 10 grams daily by mouth, was followed by a rapid and progressive disappearance of the abnormal laboratory findings.

The withdrawal of salicylate in the sixth week was followed by a rheumatic exacerbation four days later with a return of first degree heart block. The response to oral doses of 10 grams sodium salicylate daily was prompt and recovery was progressive.

The factors essential for the production of the rheumatic reaction were present in these four patients when salicylate therapy was discontinued. Although the rheumatic process was demonstrated to be present, these patients showed no clinical or laboratory signs of continued inflammation. The findings indicated not only that there was an association between the elevation of the plasma salicylic acid level to 368 gamma per cc. and the suppression of the inflammatory process but also that there was an association between the fall of the plasma level below 100 gamma per cc. and renewed rheumatic inflammation.

A PROPOSED THERAPEUTIC TECHNIQUE FOR THE USE OF SODIUM SALICYLATES IN RHEUMATIC FEVER

If one accepts the elevation of the blood sedimentation rate as an expression of inflammation in rheumatic fever, therapeutic measures which will reduce the sedimentation rate to normal as quickly as possible are indicated. One can not expect a markedly elevated sedimentation rate to reach normal limits within a week because the inflammatory reaction existing prior to treatment has already induced the elaboration of serum globulins which give rise to the accelerated rate of sedimentation of erythrocytes in rheumatic fever (9). If one can modify the sedimentation rate curve so that it ceases to rise after 72 hours of treatment and then falls progressively, reaching normal values within 14 days, there is good reason to believe that the rheumatic reaction has been suppressed and that further cardiac damage will be inhibited. To this end the following schedule of therapy is

suggested with the realization that modification will probably be forthcoming as the series of cases so treated becomes larger.

Day 1: 10 grams of sodium salicylate in 1000 cc. of 0.9 per cent NaCl are administered by intravenous drip in four to six hours.

Day 2: If the patient has any rheumatic symptoms or if the temperature has not reached normal—20 grams of sodium salicylate are administered in 2,000 cc. of 0.9 per cent NaCl in 8 hours.

Day 3: This can be repeated if necessary, but with the patient symptom-free and afebrile 10 grams of sodium salicylate are adequate.

Day 4 to 6: Sodium salicylate infusions are continued daily until the blood sedimentation rate has made an appreciable drop; e.g. about 20%.

Day 7 to 30: Oral therapy replaces intravenous treatment. Doses of 1.6 grams of sodium salicylate and 0.6 grams of sodium bicarbonate are administered every four hours day and night. A total of 10 grams of sodium salicylate is given daily during this period.

Day 30: After two weeks or more in which the sedimentation rates remain within normal limits, the patient is allowed a trial week at bed rest without any salicylate. If he remains symptom-free and maintains a normal sedimentation rate for one week he is allowed up progressively and disposition is as previously outlined (6). If however, the patient develops frank symptoms, fever or a marked rise in the blood sedimentation rate during this test week, another two weeks course of therapy is indicated. This course is either begun with oral medication or one intravenous infusion of 10 grams followed by oral doses as outlined above.

Frequent blood sedimentation rates are essential for guiding this course of treatment. In this study the Westergren method was used at the bedside and proved simple and adequate. Occasional plasma salicylic acid determinations are also useful. This check led to the discovery that one patient in the present group was discarding his drug and that another was receiving twice the dose ordered. Furthermore it is important to know: (a) whether the plasma salicylate levels to be expected with either intravenous or oral administration of the drug are attained, and (b) whether the level required for protection of the patient is maintained. There may be occasional cases that excrete the drug rapidly, conjugate it abnormally or fail to absorb it properly.

And in these unusual cases it may be necessary to combine therapeutic techniques in order to build up the desired plasma levels.

DISCUSSION

The factor of infection which is an essential component of the rheumatic reaction is apparently not modified by salicylate therapy. And so long as this factor is active the rheumatic patient is subject to inflammatory reactions. These inflammatory reactions occur in vascular tissues throughout the body and the degree and duration of inflammation in the heart determines the extent of myocardial damage and chronic valvular heart disease. The observations presented in this paper indicate that the inflammatory reaction of rheumatic fever can be suppressed to a degree that the disease process is not detectable by clinical or laboratory examinations and suggest that the prompt suppression of rheumatic inflammation may prevent the development of the stigmata of heart disease. This effect appears to parallel and be dependent upon the concentration of salicylate in the circulating plasma. As in the case of in vitro experiments (3) dealing with antigen-antibody precipitation, relatively high concentrations of free salicyl radicle are essential for modifying the reaction. Furthermore, as in these in vitro experiments it appears that the greater the concentration of circulating antibody globulin the higher is the plasma salicylate level required. Salicylate concentrations between 100 and 200 gamma per cc. of plasma may relieve all symptoms without suppressing rheumatic inflammation. Plasma levels of 600 gamma may be required to break an intense reaction at the height of the attack and maintenance levels of about 368 gamma per cc. appear to be adequate for continued suppression of the rheumatic reaction. It is realized that this series of patients is small and that in some cases the disease may have subsided spontaneously after a monocyclic attack. Nevertheless, the results warrant the extension of the therapeutic technique to a larger group of rheumatic patients.

In conclusion it is emphasized that salicylic acid is not the final solution to the therapeutic problems occurring in rheumatic fever. With the development of blood level methods other drugs may be found to be more effective in suppressing the rheumatic reaction but like salicylic acid these too may not modify the duration of rheumatic

activity. To effect this, one of two objectives must be realized. Either the immune response of the host must be modified so that the patient recovers promptly after a monocyclic attack or the capacity of the infecting microörganism to elaborate antigen must be inhibited by a chemotherapeutic agent. Since neither of these objectives has yet been realized, one is limited to the suppression of the inflammatory process. For this purpose a high concentration of salicylate in the plasma appears to be effective. This concentration is controlled by absorption, degradation, possible localization in the tissues and excretion of the drug. The significance of these four factors has been indicated; the exact role that each plays in controlling the plasma level of the salicyl radicle remains to be determined.

SUMMARY

1. A simple method for the determination of the salicyl radicle in oxalated blood is described.

2. Data on plasma salicylate levels in relation to dosage of sodium salicylate administered to rheumatic fever patients are presented.

3. Observations on the relation of rheumatic activity to the plasma salicylate level show that twenty patients maintained at 359 to 400 gamma per cc. manifested a prompt and progressive subsidence of rheumatic inflammation and that twenty other patients with plasma levels below 250 gamma per cc. continued to manifest an active inflammatory process.

4. It is pointed out that the intravenous administration of sodium salicylate is required to obtain a rapid rise in the plasma concentration of salicylate to 400 gamma per cc. or higher.

5. A therapeutic technique for the use, first of intravenous and later oral salicylate is suggested for the rapid development and maintenance of plasma salicylate levels above 350 gamma.

6. The results of two years' experience with this technique show that none of 38 rheumatic patients treated with 10 grams of sodium salicylate daily developed valvular heart disease and that 21 out of 63 similar cases who received only small doses of sodium salicylate developed physical signs of heart disease.

7. The observations suggest that a plasma salicylate level of at least 350 gamma per cc. may be required to suppress the rheumatic

reaction and that plasma levels below 200 gamma per cc. may be sufficient to relieve symptoms while masking a progressive inflammatory process.

This application of salicylate therapy to the rheumatic problem in the U. S. Navy is a continuation of work initiated in the Department of Medicine of the Presbyterian Hospital and Columbia University. The method for determining salicylate in plasma was developed in the laboratories of the Research Service, Third Medical Division of New York University College of Medicine. The author is deeply indebted to Dr. B. B. Brodie of New York University and to Drs. W. W. Palmer and A. R. Dochez of Columbia University whose help over many years made possible the present study.

BIBLIOGRAPHY

1. Coburn, A. F., and Pauli, R. H.: J. Exp. Med., 1939, **69,** 143.
2. Lutwak-Mann, Cecilia: Biochem. J., 1942, **36,** 706.
3. Coburn, A. F., and Kapp, E. M.: J. Exp. Med., 1943, **77,** 173.
4. Kapp, E. M., and Coburn, A. F.: J. Biol. Chem., 1942, **145,** 549.
5. Hanzlik, P. J., Scott, R. W., and Thoburn, T. W.: J. Pharm. and Exp. Therap., 1917, **9,** 247.
6. Coburn, A. F.: U. S. Naval Bulletin 1943, **41,** 1324.
7. Green, C. A.: J. of Hygiene, 1942, **42,** 371.
8. Brodie, B. B., Udenfriend, S., and Coburn, A. F.: In press, J. Pharm. and Exp. Therap.
9. Coburn, A. F., and Kapp, E. M.: J. Clin. Invest., 1936, **15,** 715.

ON THE ANAPHYLACTIC NATURE OF RHEUMATIC PNEUMONITIS

ARNOLD R. RICH AND JOHN E. GREGORY

From the Department of Pathology and Bacteriology, The Johns Hopkins Medical School

We have recently shown that cardiac lesions, involving the myocardium, valves and pericardium, and having the basic characteristics of those of rheumatic fever, can be produced experimentally as a reaction of anaphylactic hypersensitivity to foreign protein (1). In that report we drew attention to the fact that a wide variety of lesions (erythemas, urticaria, purpura, arthritis, transient pareses, myocarditis, valvulitis, pericarditis, focal swelling and degeneration of collagen, tissue eosinophilia, necrosis and inflammation of arteries) are common both to rheumatic fever and to the anaphylactic reaction of human or experimental serum sickness. These circumstances were discussed in relation to the possibility that the lesions of rheumatic fever may be the results of an anaphylactic reaction to some foreign antigen, such as a product of the haemolytic streptococcus. We have since, in common with Bruun (2), observed the occurrence of acute arthritis during the course of prolonged, systemic anaphylactic reactions in animals. The occurrence of arthritis, often indistinguishable from the arthritis of rheumatic fever, is, of course, familiar in human serum sickness.

The purpose of the present paper is to draw attention to the basic identity of the pulmonary lesions of rheumatic fever with those resulting from anaphylactic hypersensitivity, and so to add this additional evidence to that already cited in support of the view that the lesions of rheumatic fever may be anaphylactic in origin.

The occurrence of a peculiar pulmonary lesion in association with some cases of acute rheumatic fever has been described by numerous writers and is now a familiar pathological observation. Excellent descriptions (with literature) can be found in the papers of Epstein and Greenspan (3) and Gouley and Eiman (4). Briefly, a careful study of the process shows that the primary alteration is a focal damage to the alveolar capillaries. In its mildest form the capillary damage is manifested only by an exudation of fluid into the related alveolar

spaces, but leucocytes often infiltrate the alveolar wall about the affected capillary, and also escape into the alveoli in numbers varying from a very few to a great many. Focal necrosis of the capillary endothelium may occur, and the lumen may become plugged with a fibrinous or hyaline thrombus. Sometimes the capillary damage permits the occurrence of intra-alveolar haemorrhages. Often the respiratory bronchioles and their adjacent alveoli become lined with an eosinophilic, hyaline membrane. Focal necrosis of the entire alveolar wall may occur where the capillary damage is severe. The lesions are decidedly focal, sometimes affecting only a segment of one capillary in an entire low-power field, though they often involve the vessels of a sufficient number of adjacent alveoli to produce confluent areas of consolidation. The affected portions of the lung are sterile on culture and contain no micro-organisms stainable in the sections. The above histological characteristics of rheumatic pneumonitis are illustrated in Figures 1, 3, 5, 7, 9, 11 and 13. In later stages the exudate or haemorrhage may undergo organization.

The cause of this peculiar, focal rheumatic pneumonitis has remained obscure. In view of our recent experimental studies indicating the anaphylactic nature of the rheumatic cardiac lesions (1), we have re-examined a series of cases of rheumatic pneumonitis from the standpoint of comparing this lesion with that of an anaphylactic pneumonitis, namely, that which results from hypersensitivity to the sulfonamides.

It has been pointed out by Lederer and Rosenblatt (5) and by Merkel and Crawford (6) that a peculiar, focal pulmonary lesion occurs in some patients during treatment with sulfathiazole. One of us (8) has called attention to the fact that this lesion is primarily a vascular one, and has presented evidence that it is a result of hypersensitivity to the drug.[1] We have, therefore, carefully compared this pneumonitis of hypersensitive origin in five patients without rheumatic fever (Autopsies 17529, 17895, Outside CH 42, Outside UM, Outside PH) with that associated with seven cases of rheumatic fever with acute cardiac lesions (Autopsies 13013, 13570, 14462, 16401, 16720,

[1] A paper by Shaffer, Lentz and McGuire has just appeared, in which the authors report the demonstration of the hypersensitive nature of the sulfathiazole eruptions by means of passive transfer tests (Journ. A. M. A., 1943, **123,** 17).

17922, 18271). Five of these rheumatic cases had received no sulfonamide therapy. One had been given a single dose of sulfapyridine, that was promptly vomited, seven days before death and no further sulfonamide was administered. One other was given sulfapyridine only during the last 48 hours of life. It is, of course, altogether unlikely that sulfapyridine hypersensitivity could have occurred in either of these two cases, in which a well developed pneumonitis, quite like that in the five rheumatic cases untreated with sulfonamides, was present.

The comparison of the lesions in the cases of rheumatic pneumonitis with those of sulfonamide anaphylactic pneumonitis in the absence of rheumatic fever has revealed that the pulmonary lesions in these two conditions are basically identical histologically. As in the case of rheumatic pneumonitis, the primary pulmonary lesion of sulfathiazole hypersensitivity is a capillary damage, with exudation of fluid and leucocytes; focal haemorrhages occur; there is focal necrosis of the endothelium of the alveolar capillaries, with thrombosis; focal necrosis of the alveolar wall occurs; a hyaline membrane lines some of the alveoli; and no bacteria are demonstrable in the lesions by stain or culture. Figures 2, 4, 6, 8, 10 and 12 will serve to illustrate the basic identity of this anaphylactic lesion with that of rheumatic pneumonitis. As in the case of the rheumatic lesions, in later stages organization of some of the focal haemorrhages and exudates may occur. In our material the individual pulmonary lesions of sulfonamide hypersensitivity tend to occupy a smaller area than do the rheumatic lesions. This may conceivably be related to the fact that, because of the passive congestion of heart failure, areas of pulmonary oedema were present in the rheumatic cases, and the passage of antigen and antibody through the pulmonary capillary endothelium, providing an opportunity for their meeting there, could be furthered by this circumstance.

DISCUSSION

As was stated above, careful study of the lesions of rheumatic pneumonitis shows that the primary injury is a focal damage to the alveolar capillaries. This conclusion was reached by Epstein and Greenspan (3), and by Gouley and Eiman (4), and with that conclusion our studies are in complete agreement. The primary nature of the capillary damage is emphasized by the fact that it is often altogether

out of proportion to the degree of cellular exudation. Thrombosed capillaries may be found in the walls of alveoli that are almost free from cellular exudate (Fig. 3).

Similarly, capillary damage constitutes the primary injury in the anaphylactic pneumonitis, as is clearly evident from the accompanying illustrations. Indeed, it is well known that capillary damage, varying from increased permeability with exudation of fluid to necrosis of the endothelium, haemorrhage or thrombosis, is a characteristic local anaphylactic effect wherever the sensitizing antigen and its antibody meet in vascular tissues (13). The urticarial wheal and the Arthus phenomenon are familiar examples of this fact. Rich and Follis (12) have shown that the necrosis of tissue cells at the site of the Arthus phenomenon is really secondary to capillary damage. It is also well known that when the antigen is distributed throughout the sensitized body by the blood stream, focal capillary endothelial damage, often multiple, may occur (urticaria; purpura).

We have, furthermore, shown from clinical-pathological material (7, 8), and experimentally (9), that the sharply focal vascular lesions of periarteritis nodosa can be produced by a foreign antigen circulating in the blood stream of the anaphylactically sensitized body, and that here, too, the earliest visible damage is a focal injury to the endothelium. We have reported a case in which both periarteritis nodosa and pneumonitis of the type under discussion occurred as a result of a sulfonamide hypersensitive reaction (8), and we have seen several other cases of sulfonamide reaction in which both of these anaphylactic manifestations of vascular damage occurred.

In rheumatic fever, focal damage of the periarteritis nodosa type (so-called "rheumatic arteritis") is well known to be not infrequent (11), and focal damage to the cutaneous capillaries (urticaria; erythemas; purpura) is familiar in this disease. Rheumatic pneumonitis appears to be merely the result of a similar focal, anaphylactic capillary damage occurring in the lung. Its characteristics suggest that it may represent the pulmonary analogue of the cutaneous urticaria, erythemas and purpura that occur in rheumatic fever and in a wide variety of anaphylactic conditions.

Gouley and Eiman (4) have commented upon the presence of "large, deeply stained cells, with vesicular nuclei, often multinuclear and markedly basophilic", in the lung in rheumatic pneumonitis. They

regarded these cells as identical with those familiar in the Aschoff body. In our material cells of this type are only occasionally encountered in the lungs. It is of interest, however, that cells of precisely the same type occur occasionally in the sulfonamide anaphylactic pneumonitis also (Fig. 14). Large, basophilic, multinuclear cells of this type were likewise present in the anaphylactic cardiac lesions of our experimental animals (1).

It is also of interest that in one of our cases of rheumatic pneumonitis (Autopsy 16401) and in one of our cases of sulfonamide anaphylactic pneumonitis (Autopsy 17895) the lesions contain abundant eosinophils. The relation of eosinophils to anaphylactic reactions is familiar, and we have called attention to their presence in the heart in a considerable proportion of the very acute cases of rheumatic carditis (1). That they are not present in all cases of anaphylactic pneumonitis is paralleled by the fact that they are present in some but not in all anaphylactic urticarial lesions (10).

Why this type of pneumonitis does not occur in all cases of acute rheumatic fever with cardiac involvement remains as obscure as why urticaria or vascular lesions of the periarteritis nodosa type occur in some (11) but not in all cases of rheumatic carditis, or why hypersensitivity to a given pollen causes asthma in some patients, hay fever in others, and in some patients both of these conditions.

SUMMARY

In preceding papers we have shown that cardiac and arterial lesions having the basic characteristics of those of acute rheumatic fever can be produced experimentally as a result of anaphylactic hypersensitivity. The present comparison of the peculiar lesion of rheumatic pneumonitis with that of the pneumonitis caused by sulfonamide hypersensitivity shows that the two are basically identical, and that both exhibit the primary capillary damage characteristic of focal anaphylactic reactions. This provides additional evidence in support of the view that the lesions of acute rheumatic fever may be anaphylactic in origin.

REFERENCES

1. Rich, A. R., and Gregory, J. E.: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. Bull. Johns Hopkins Hosp., 1943, **73**: 239.

2. Bruun, E.: Experimental Investigations in Serum Allergy. Copenhagen, 1940.
3. Epstein, E. Z., and Greenspan, E. B.: Rheumatic pneumonia. Arch. Int. Med., 1941, **68,** 1074.
4. Gouley, B. A., and Eiman, J.: The pathology of rheumatic pneumonia. Am. J. Med. Sc., 1932, **183,** 359.
5. Lederer, M., and Rosenblatt, P.: Death during sulfathiazole therapy. Jour. A. M. A., 1942, **119,** 8.
6. Merkel, W. C., and Crawford, R. C.: Pathologic lesions produced by sulfathiazole. Jour. A. M. A., 1942, **119,** 770.
7. Rich, A. R.: The rôle of hypersensitivity in periarteritis nodosa, as indicated by seven cases developing during serum sickness and sulfonamide therapy. Bull. Johns Hopkins Hosp., 1942, **71,** 123.
8. Rich, A. R.: Additional evidence of the rôle of hypersentivity in the etiology of periarteritis nodosa. Another case associated with a sulfonamide reaction. Bull. Johns Hopkins Hosp., 1942, **71,** 375.
9. Rich, A. R., and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. Bull. Johns Hopkins Hosp., 1943, **72,** 65.
10. Torok, L., and Lehner, E.: Zur Anatomie und Pathogenese der Urticaria. Arch. f. Derm. u. Syph., 1921, **132,** 401.
11. Friedberg, C. K., and Gross, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease. Arch. Int. Med., 1934, **54,** 170.
12. Rich, A. R., and Follis, R. H., Jr.: Studies on the site of sensitivity in the Arthus phenomenon. Bull. Johns Hopkins Hosp., 1940, **66,** 106.
13. Rich, A. R.: The significance of hypersensitivity in infections. Physiol. Rev., 1941, **21,** 70.

EXPLANATION OF ILLUSTRATIONS

(Photographs by Miss Dorothy Schmitt)

FIG. 1. Rheumatic pneumonitis. Thrombosis of segment of capillary in alveolar wall (Autopsy 18271).

FIG. 2. Sulfonamide anaphylactic pneumonitis. Thrombosis of segment of capillary in alveolar wall (Autopsy Outside CH 42).

Fig. 3. Rheumatic pneumonitis. Capillary thrombosis with necrosis of segment of alveolar wall (Autopsy 18271).

FIG. 4. Sulfonamide anaphylactic pneumonitis. Capillary thrombosis with necrosis of segments of alveolar walls (Autopsy Outside CH 42).

FIG. 5. Rheumatic pneumonitis. Capillary thrombosis with necrosis of segment of alveolar wall (Autopsy 18271).

FIG. 6. Sulfonamide anaphylactic pneumonitis. Capillary thrombosis with necrosis of segment of alveolar wall (Autopsy Outside CH 42).

FIG. 7. Rheumatic pneumonitis. Hyaline membrane lining an alveolus (Autopsy 18271).

FIG. 8. Sulfonamide anaphylactic pneumonitis. Hyaline membrane lining an alveolus (Autopsy Outside CH 42).

FIG. 9. Rheumatic pneumonitis. Haemorrhage into alveoli (Autopsy 16401).

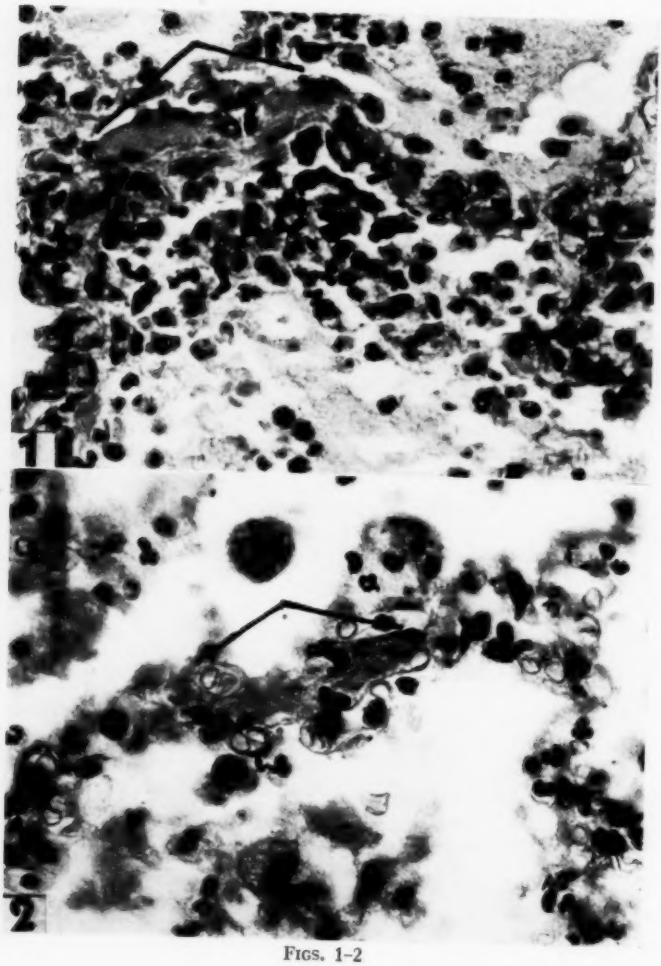
FIG. 10. Sulfonamide anaphylactic pneumonitis. Haemorrhage into alveoli (Autopsy 17895).

FIG. 11. Rheumatic pneumonitis. Sharply focal cellular exudate, filling a single alveolus. Very slight cellular exudation in surrounding alveoli (Autopsy 18271).

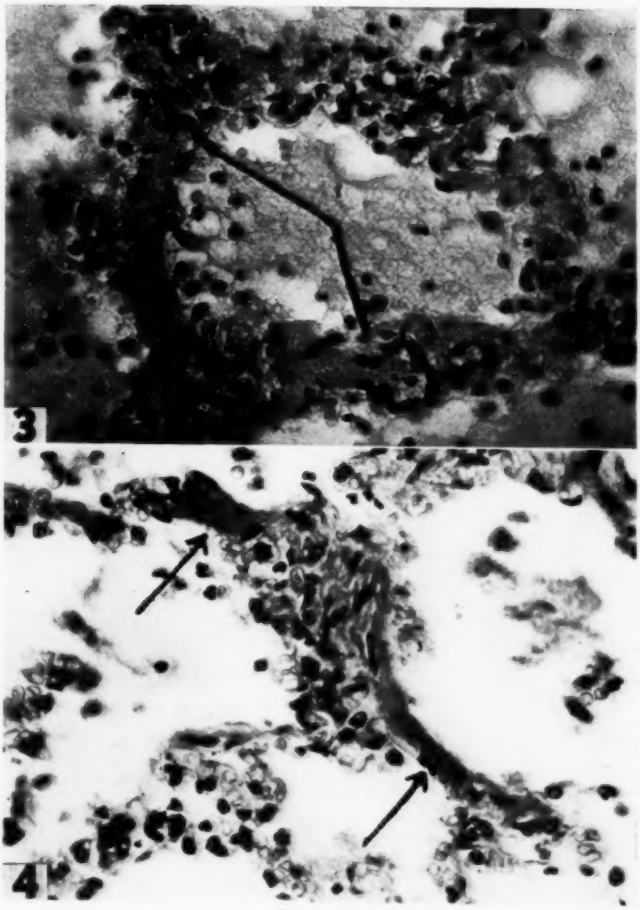
FIG. 12. Sulfonamide anaphylactic pneumonitis. Sharply focal cellular exudate filling a single alveolus. Very slight cellular exudation in surrounding alveoli (Autopsy Outside CH 42).

FIG. 13. Rheumatic pneumonitis. Necrosis of top segment of alveolar wall (Autopsy 18271).

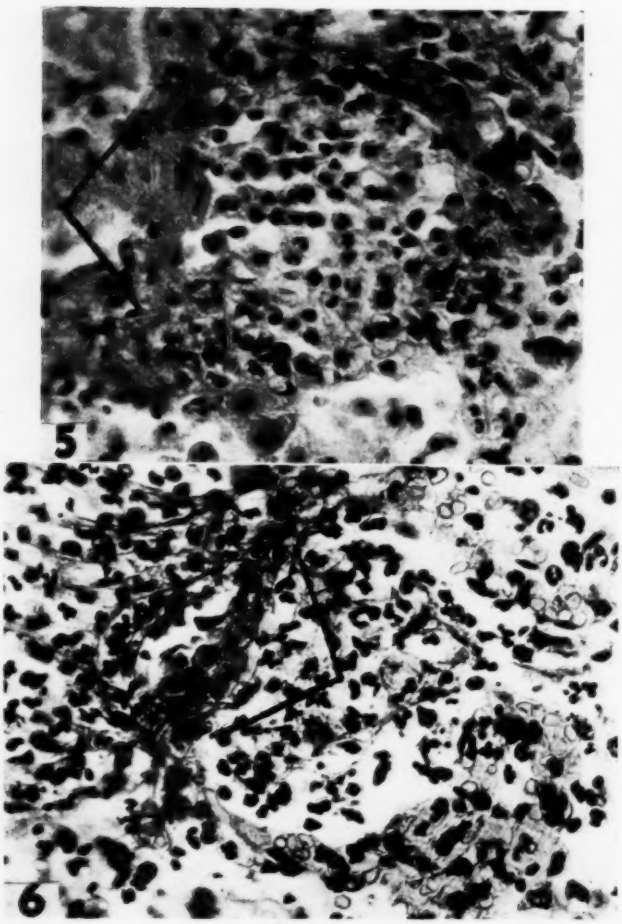
FIG. 14. Sulfonamide anaphylactic pneumonitis. Large, basophilic multinuclear cell in organizing alveolar exudate (Autopsy 17895).



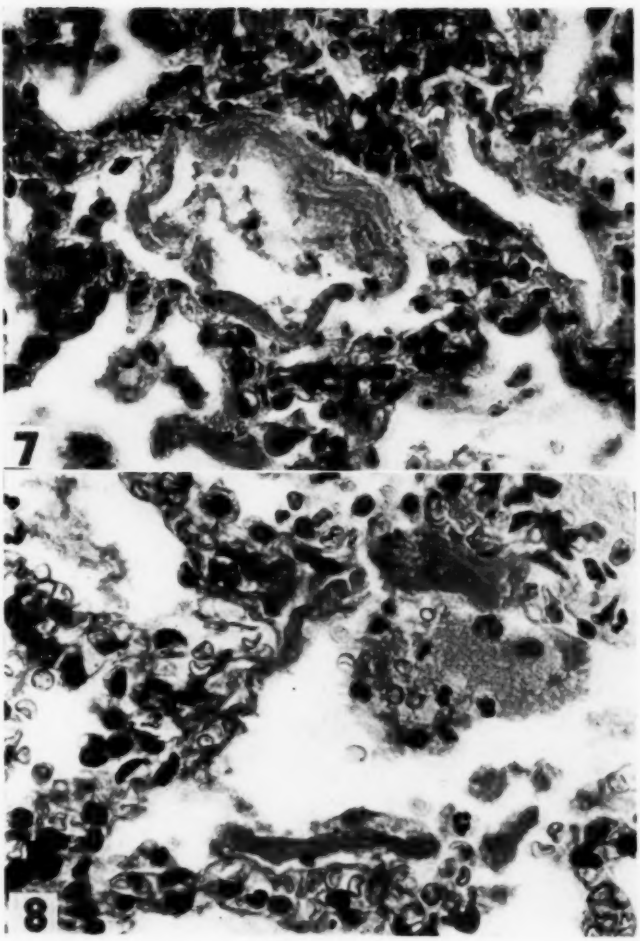
FIGS. 1–2



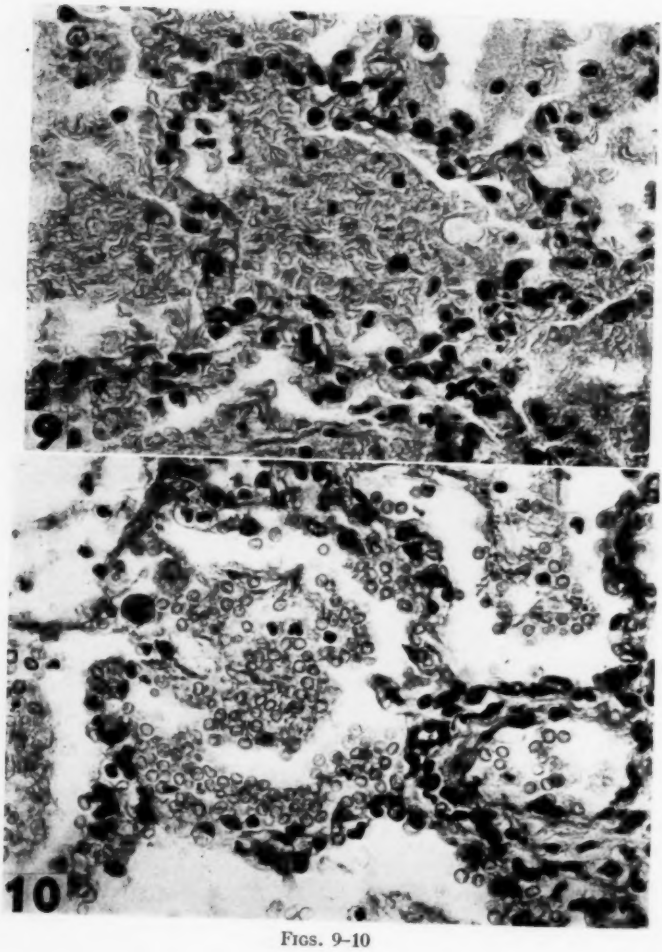
FIGS. 3–4



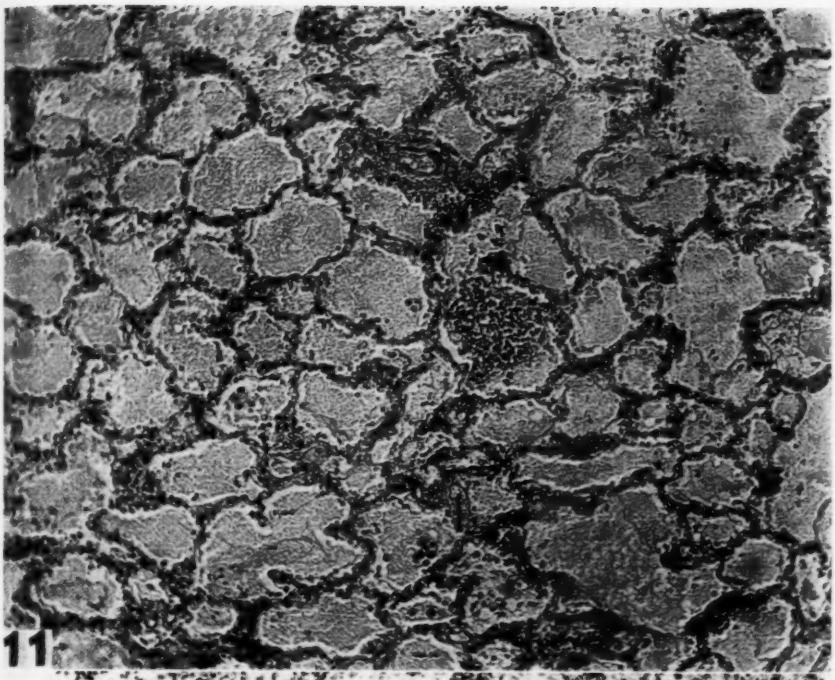
FIGS. 5-6



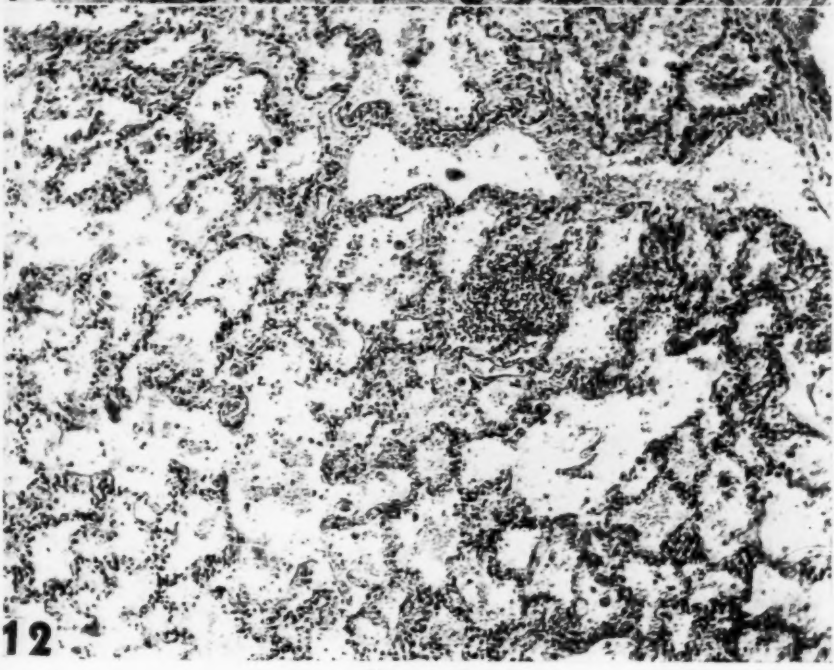
FIGS. 7–8



FIGS. 9–10

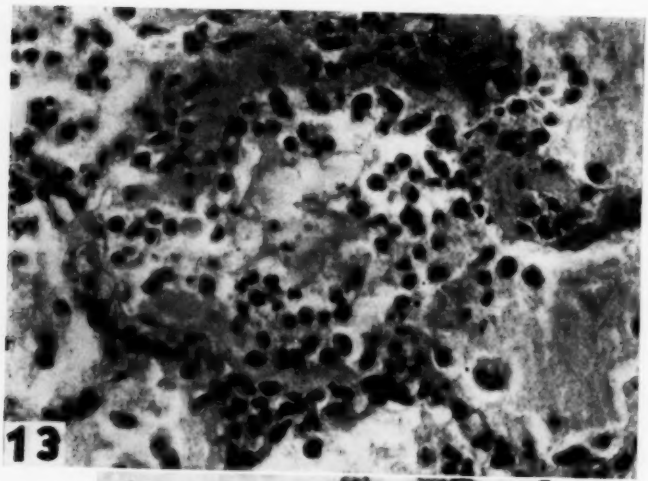


11



12

FIGS. 11–12



FIGS. 13–14

SODIUM PROPIONATE IN THE TREATMENT OF SUPERFICIAL FUNGOUS INFECTIONS[1]

EDMUND L. KEENEY, M.D.

Baltimore, Md.

AND

COMDR. EDWIN N. BROYLES (MC)

U.S.N.R.

"Mycoban" (trade name of the E. I. DuPont de Nemours Company for sodium or calcium propionate) is incorporated in bread dough and cake batter, by many of the large baking companies, to inhibit the growth of molds. Hoffman, Schweitzer and Dalby (1) have demonstrated that many of the fatty acids and their salts are fungistatic for some of the non-pathogenic fungi. The retarding effect of sodium and calcium propionate on molds in dairy products has been extensively investigated by Miller (2), Irvine and Spraule (3), Ingle (4), and Macy and Olson (5). Peck and Rosenfeld (6) working with Trichophyton gypseum, Epidermophyton inguinale, and Monilia (Candida) albicans have demonstrated fungistatic action for sodium propionate at a pH of 5.6. Recently Keeney (7) demonstrated that sodium propionate adjusted at pH 5.5 was fungistatic for all of the common pathogenic fungi.

The work of Rowntree (8), Desgrez and Saggio (9), and Harshbarger (10), and the fact that the propionates have been incorporated in bread dough and cake batter for human consumption suggested to us that the propionates were not toxic.

Because of these data it occurred to us that sodium propionate might be effective in the treatment of superficial fungous infections. A 10 per cent sodium propionate ointment, powder and solution were pre-

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins University.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

pared.[2] The in vitro experiments of Keeney (7) assisted us in selecting the concentration and the hydrogen-ion concentration of sodium propionate that was most likely to be effective for clinical experimentation.

Patients with athlete's foot (tinea pedis), tinea cruris, tinea capitis, tinea glabrosa, otomycosis, thrush, and black tongue were selected for study. Scrapings from the affected areas on each patient were made for direct examination of fungous material and for culture before treatment was initiated and at periodic intervals, thereafter, whenever it was possible.

CLINICAL RESULTS

Athlete's foot (*Tinea pedis*). Fifty-five midshipmen from the United States Naval Academy with athlete's foot were treated and observed at regular intervals for a period of 20 weeks. Because of the variation in the degree of infection the cases were classified at the onset of the investigation as minimal, moderately advanced and advanced. Notations were made as to the character of the lesion between the toes, i. e. the existence of maceration, fissuring, intertrigo and denudation. However, to simplify the classification we have inferred the presence of one or a combination of any of these lesions by using the term "web involvement." Cases described as minimal had a total of 1 to 2 webs involved or had vesicular lesions on the soles without web involvement. Cases classified as moderately advanced had a total of 2 to 4 webs involved or had 1 to 2 webs involved with vesicular lesions on the soles. The advanced cases had lesions in excess of those classified as moderately advanced.

Fungous material was found from scrapings by direct examination in 3 of the 17 minimal cases, in 4 of the 22 moderately advanced cases and in 4 of the 17 advanced cases. Trichophyton purpureum was isolated from the cultures in 2 of the 3 cases of the minimal group that showed fungous material by direct examination, and in 3 of the 4 cases of the moderately advanced group that showed fungous material by

[2] The sodium propionate ointment, solution and powder were generously supplied by The Mycoloid Laboratories, Inc., Little Falls, N. J.

We are greatly indebted to the authorities of the United States Naval Academy. Their interest and complete cooperation made this study possible.

direct examination. Trichophyton gypseum was isolated in 2 cases and Trichophyton purpureum in 2 cases of the 4 cases of the advanced group that showed fungous material by direct examination.

The following scheme of treatment was observed. The feet were washed each night with soap and water and then dried thoroughly. The ointment was rubbed well into the skin between the toes and on the soles of the feet. The following morning the feet were washed again and after drying the powder was dusted between the toes and on the soles of the feet. If washing of the feet was impossible the patients were advised to remove the ointment with a towel before applying the powder. The powder was placed in all of the shoes and slippers two times a week.

TABLE 1

Observations on the Effectiveness of a 10 Per Cent Sodium Propionate Ointment and Powder in the Treatment of Athlete's Foot

No. of Cases	Types of Cases	After 2 Weeks' Treatment						After 4 Weeks' Treatment						After 8 Weeks' Treatment						After 12 Weeks' Treatment						After 16 Weeks' Treatment						After 20 Weeks' Treatment					
		No. of Cases	Condition in Percentage					No. of Cases	Condition in Percentage					No. of Cases	Condition in Percentage					No. of Cases	Condition in Percentage					No. of Cases	Condition in Percentage					No. of Cases	Condition in Percentage				
			* W	= S	↑ I	↓ C	± R		W	S	I	C	R		W	S	I	C	R		W	S	I	C	R		W	S	I	C	R		W	S	I	C	R
17	Minimal	13	0	8	54	8	0	10	0	0	50	50	0	15	0	0	18	82	0	10	0	0	10	90	0	12	0	0	0	100	0	8	0	0	0	88	12
22	Moderately Advanced	19	5	16	68	11	0	17	0	0	59	24	17	17	0	0	11	72	17	13	0	15	0	77	8	17	0	6	0	94	0	14	0	0	0	79	21
16	Advanced	13	7	8	54	31	0	10	0	0	56	44	0	11	0	0	10	90	0	9	0	0	0	78	22	10	0	0	30	70	0	8	0	0	0	73	25

* Worse = Same ↑ Improved ± Clear ± Recurred

The results of the survey are summarized in Table 1. In the group with minimal lesions, all of the slides prepared for the direct examination of fungous material were negative and all of the cultures were sterile after 4 weeks of treatment. In the group with moderately advanced lesions, after 4 weeks of treatment, 2 cases persisted in showing positive slides for fungous material and from 1 of these cases we were still able to obtain a culture of Trichophyton purpureum. In the group with advanced lesions, after 4 weeks of treatment, 1 case persisted in showing a positive slide for fungous material and a culture of Trichophyton purpureum. After 8, 12 and 16 weeks of treatment only 1 case in the moderately advanced group revealed a positive slide for fungous material and a culture of Trichophyton purpureum. All of the cases in the minimal and advanced groups revealed negative slides for fungous material and sterile cultures. After 16 weeks of

treatment the men became careless in observing the routine of treatment and in the ensuing 4 weeks there were some recurrences (see Table 1). At the end of 20 weeks of treatment, 1 positive slide for fungous material was obtained in each of the groups but only 1 positive culture was obtained and that was in the 1 case in the moderately advanced group that had remained resistant to therapy during the entire period of observation.

There was no evidence that the sodium propionate was irritating. This is particularly significant in view of the fact that applications of the ointment and the powder were made daily for a period of 20 weeks. One patient developed a contact dermatitis from the sodium propionate and treatment had to be discontinued. This patient gave a positive patch test to the sodium propionate ointment and the sodium propionate powder.

Tinea cruris. Twenty-three midshipmen from the United States Naval Academy with typical tinea cruris were treated and observed at regular intervals for a period of 12 weeks. Fungous material was found by direct examination in 13 cases and from these 9 positive cultures were obtained. Each culture revealed Epidermophyton inguinale.

The following scheme of treatment was observed. The ointment was rubbed well into the affected areas of the skin every night. The following morning the ointment was removed and the affected parts were dusted liberally with the powder. It was suggested that the powder be used after every bath. No attempt was made to limit activities or issue new wearing apparel.

After 2 weeks of treatment 36 per cent of the cases were cured, 59 per cent of the cases were improved and 5 per cent of the cases remained the same. After 4 weeks of treatment 68 per cent of the cases were cured, 22 per cent of the cases were improved, 9 per cent of the cases were the same and 1 per cent of the cases were worse. There was no evidence that the ointment and powder had been irritating in those cases that were worse but it was the feeling of all of the observers that the method of treatment had been unsatisfactory. After 8 weeks of treatment 77 per cent of the cases were cured, 14 per cent of the cases were improved, 4.5 per cent of the cases were the same, and 4.5 per cent of the cases had recurred. After thoroughly questioning the

group with recurrences it was found that in each instance the patient had failed to observe the scheme of treatment. After 12 weeks of treatment 91 per cent of the cases were cured and 9 per cent of the cases showed only a slight trace of the infection.

At the end of 4 weeks of treatment fungous material was found by direct examination in only 3 patients. Cultures taken from each of these patients revealed Epidermophyton inguinale. At the end of 8 and 12 weeks of treatment all of the slides were negative for fungous material and all of the cultures were sterile.

Miscellaneous Observations. Two patients with otomycosis, in whom repeated cultures from both external auditory canals had revealed Aspergillus fumigatus, had been treated unsuccessfully in the Nose and Throat Dispensary of the Johns Hopkins Hospital with thymol, cresatin and a 2 per cent solution of salicylic acid in a 90 per cent solution of ethyl alcohol. Fungistatic experiments performed with sodium propionate and the cultures obtained from these patients revealed that a 1.25 per cent solution of sodium propionate adjusted at pH 5.5 completely inhibited the growth of the fungi. The following scheme of treatment with sodium propionate was instituted. Three times each week the external auditory canals were thoroughly cleaned and then swabbed with a 10 per cent aqueous solution of sodium propionate adjusted at pH 5.5. After the solution had dried the pure sodium propionate powder was insufflated into each auditory canal. After 2 weeks of treatment the patients were clinically well and the cultures from both patients were sterile. Similar results were obtained in one patient with otomycosis in whom repeated cultures from both external auditory canals had revealed Aspergillus flavus.

One patient with an eczema of both external auditory canals was seen in the private offices of one of us (E. L. K.). A clinical diagnosis of fungous infection of the external auditory canals, possibly due to Aspergillus niger, had been made by an oto-laryngologist. Cultures from both external auditory canals revealed Aspergillus niger. Treatment with sodium propionate, as outlined above, was carried out for 4 weeks and at the end of this time the cultures were sterile but the condition of the eczema had remained unaltered.

One 3 month old infant presenting the typical clinical picture of thrush was seen in the outpatient department of the Harriet Lane

Home for Invalid Children of the Johns Hopkins Hospital. Cultures taken from the lesions in the mouth revealed Monilia (Candida) albicans. A 20 per cent aqueous solution of sodium propionate adjusted at pH 7.0 was prepared and the mother was instructed to swab the mouth with this solution three times daily. After 7 days of treatment the infant was completely well and the cultures were sterile.

Two adult patients with tinea glabrosa involving the trunk and the extremities were seen in the outpatient department of the Johns Hopkins Hospital. Cultures from one of the patients revealed Trichophyton purpureum. Cultures from the second patient were sterile and fungous material could not be demonstrated by direct examination. However, it was the impression of all observers that the patient had a cutaneous fungous infection. The patient with the positive culture of Trichophyton purpureum was instructed to apply tincture of iodine (1 per cent) once daily to the lesions on the left arm and the left leg and the sodium propionate ointment twice daily to the lesions on the right arm and the right leg and trunk. After 1 week of treatment all of the lesions were improved but the lesions treated with the tincture of iodine had improved more than those treated with the sodium propionate ointment. After 2 weeks of treatment there was similar improvement in all of the lesions. However, the skin treated with the tincture of iodine was dry and irritated while the skin that had been treated with the sodium propionate ointment was of normal texture. After 3 weeks of treatment the superior efficacy of the sodium propionate ointment was so evident that the tincture of iodine was discontinued and the sodium propionate ointment was applied to all of the lesions on the body. After 4 weeks of treatment the patient was well. Cultures taken from lesions on the right and left arms after 2 and 4 weeks of treatment were sterile. No fungous material was found by direct examination. The second patient was treated only with the sodium propionate ointment and was instructed to apply the ointment to all of the affected areas twice daily. The patient was completely well in 2 weeks. A third patient, a 7 year old colored boy, with a circinate type of lesion on the right cheek, was seen in the outpatient department of the Harriet Lane Home for Invalid Children of the Johns Hopkins Hospital. Fungous material was found on direct examination and cultures taken from the lesion revealed Microsporum

audouini. The parents of the patient were instructed to apply the sodium propionate ointment to the affected area on the right cheek, three times daily. After 5 days of treatment the lesion had completely disappeared. Therapy was discontinued and when the child was last seen, 7 weeks after therapy had been discontinued, there had been no recurrence.

Three children with tinea capitis due to Microsporum audouini were seen in the outpatient department of the Harriet Lane Home for Invalid Children of the Johns Hopkins Hospital. The parents of the patients were instructed to apply the sodium propionate ointment to the affected areas three times daily. The children were not seen again until 7 weeks had elapsed. At this time 2 of the children were completely well and their parents stated that the lesions had disappeared after 3 weeks of treatment. Fungous material could not be found by direct examination and the cultures were sterile. The third child remained the same and was not improved. The lesions, however, had not progressed. Fungous material was found by direct examination and the cultures still revealed Microsporum audouini.

A 30 year old physician was seen in the private offices of one of us (E. L. K.) complaining of a black tongue of 10 months duration. The entire dorsal surface of the tongue was covered with a brownish-black filamentous growth. Filaments from the tongue were placed in thioglycollate media on 2 occasions. Each culture revealed an actinomycete. The physical examination failed to reveal any evidence of systemic disease. Laboratory examination of the blood, the urine, the gastric contents, and the stool were normal. The patient had taken large doses of nicotinic acid for 2 months without effect. Mouth washes of potassium chlorate, boric acid and sodium perborate had been tried and local applications of gentian violet had been made without relief. The patient was instructed to dust pure sodium propionate powder over the dorsal surface of the tongue 3 times daily. After 2 weeks of treatment the filamentous growth had completely disappeared and the tongue appeared normal. It has now been 6 months since treatment has been discontinued and there has been no recurrence.

Sodium propionate ointment, solution or powder has been used on 376 patients in addition to the 90 patients reported in this article.

These patients can not be reported upon at this time because of insufficient data. However, it is important to point out that these patients have used sodium propionate daily for long periods of time without evidence of irritation and without evidence of allergic manifestations to the sodium propionate.

SUMMARY AND CONCLUSIONS

Sodium or calcium propionate is incorporated in bread dough and cake batter by many large baking companies to inhibit the growth of molds. Recent in vitro studies have revealed that sodium propionate is fungistatic for the common pathogens. It occurred to us that sodium propionate might prove useful in the treatment of superficial fungous infections.

Sodium propionate prepared in an ointment, solution and powder and applied locally has appeared to be effective in the treatment, of athlete's foot due to Trichophyton gypseum and Trichophyton purpureum; of tinea cruris due to Epidermophyton inguinale; of tinea capitis due to Microsporum audouini; of tinea glabrosa due to Microsporum audouini and Trichophyton purpureum; of thrush due to Monila (Candida) albicans; of otomycosis due to Aspergillus fumigatus, Aspergillus flavus and Aspergillus niger and of black tongue due to an actinomycete.

Sodium propionate in an ointment and in a powder has been used daily by 23 patients with tinea cruris for 12 weeks and by 55 patients with athlete's foot for 20 weeks. No evidence of irritation from its constant use was observed. One patient developed a contact dermatitis from sodium propionate after 4 days of treatment.

Sodium propionate in ointment, powder or solution has been used by 376 patients, in addition to the 90 patients reported in this article, without evidence of irritation and without evidence of allergic manifestations to the sodium propionate. These patients could not be included in this report because of insufficient data.

BIBLIOGRAPHY

1. Hoffman, C., Schweitzer, T. R., and Dalby, G.: Fungistatic properties of the fatty acids and possible biochemical significance. Food Research, **4**: 539, 1939.
2. Miller, F. W.: Retarding mold in cheese. Nat. Butter and Cheese J., **8**: 31, 1940.

3. IRVINE, O. R., AND SPRAULE, W. H.: Mold inhibitors for cheese. Canad. Dairy and Ice Cream J., **19:** 19, 1940.
4. INGLE, J. D.: Some preliminary observations on the effectiveness of propionates as mold inhibitors on dairy products. J. Dairy Research, **23:** 509, 1940.
5. MACY, H., AND OLSON, J. C.: Preliminary observations on the treatment of parchment paper with sodium or calcium propionate. J. Dairy Science, **22:** 527, 1939.
6. PECK, S. M., AND ROSENFELD, H.: The effect of hydrogen ion concentration, fatty acids and vitamin C on the growth of fungi. J. Invest. Dermat., **1:** 237, 1938.
7. KEENEY, E. L.: The fungistatic and fungicidal effect of sodium propionate on common pathogens. Bull. Johns Hopkins Hospital, **73:** 379, 1943.
8. ROWNTREE, L. G.: Unpublished data.
9. DESGREZ, A., AND SAGGIO, G.: Sur la nocivité des composes actetoniques. Compt. rend. Soc. de Biol., **63:** 288, 1907.
10. HARSHBARGER, K. E.: Food preserving agents. J. Dairy Science, **25:** 168, 1942.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Biological Symposia. Volume VII. *Visual Mechanisms.* Edited by HEINRICH KLÜVER. 322 pp. Illus. $3.25. The Jaques Cattell Press, Lancaster, Pa., 1942.

This volume contains twelve papers which were prepared by investigators who are recognized as authorities in their particular fields of study. Eight of these were read at a symposium held on September 24, 1941. To make the volume more complete, the editor obtained four additional papers.

The papers are as follows: Energy Relations in Vision by S. Hecht; The Photochemistry of Visual Purple by G. Wald; Anoxia in Relation to the Visual System by E. Gellhorn; Visual Sensation and Its Dependence on the Neurophysiology of the Optic Pathway by S. H. Bartley; Alpha Waves in Relation to Structures Involved in Vision by T. J. Case; Recent Evidence for Neural Mechanisms in Vision Leading to a General Theory of Sensory Acuity by W. H. Marshall and S. A. Talbot; The Functional Organization of the Occipital Lobe by G. v. Bonin, H. W. Garol and W. S. McCulloch; Anatomy of the Retina by S. L. Polyak; The Visual Cells and their History by G. L. Walls; Functional Significance of the Geniculo-Striate System by H. Klüver; The Problem of Cerebral Organization in Vision by K. S. Lashley.

It is interesting that several papers are based on electrophysiological studies. Gellhorn's paper contained information immediately applicable as regards dilatation of the pupil associated with anoxia, and the interrelationship between anoxia and hypoglycemia both of which depress visual functions. Case concluded that interruption anywhere in the geniculocalcarine tract will interfere with the occipital alpha wave on that side. Marshall and Talbot presented evidence regarding reciprocal overlap in the transmission of visual impulses which raises a question regarding the point-to-point representation between the retina and the visual cortex.

The volume is a noteworthy contribution. It exemplifies the value of symposiums particularly when there are many points of view and an infinite variety of methods of study of the subject. Each paper contains fundamental information regarding the particular aspect with which it is concerned. Several of the papers are highly technical and over the head of the average clinician. Although they have been written with the purpose of adding fundamental knowledge rather than of pointing out clinical application, all of us can receive great benefit by study of the papers in this volume. F. B. W.

Synopsis of Ano-Rectal Diseases. By LOUIS J. HIRSCHMAN. 2nd ed. 315 pp. Illus. $4.50. The C. V. Mosby Company, St. Louis, 1942.

In this second edition of his well established handbook of proctology, which is

profusely and newly illustrated, Dr. Hirschman again covers the general field exceptionally well in his clear, concise and factual style. He has added a new and extremely interesting chapter on focal infections of ano-rectal origin. He makes no mention, however, of pilonidal sinuses or cysts, or of lymphopathia venereum, both important subjects in this field. He omits too, and purposely, according to his preface, any mention of the early symptoms, diagnosis and recognition of carcinoma of the terminal bowel, which seems unfortunate in a book, which, otherwise, would prove an excellent reference book for both student and general practitioner. Technical details of the surgical procedures advocated in the cure of ano-rectal diseases have been omitted almost entirely, and again purposely, but it is of course difficult to cover everything in a synopsis.

T. R. C.

Diseases and Injuries of the Larynx. By CHEVALIER JACKSON AND CHEVALIER L. JACKSON. 2nd ed. 633 pp. Illus. $8.00. The Macmillan Company, New York, 1942.

This is the second and revised edition of The Larynx and its Diseases, published in 1937, by the same authors. Larger type is used and the print more legible. The same text, illustrations and plates have been used with but few exceptions. Among the changes in the text is the omission of Ventriculocordectomy previously advised in the treatment of bilateral paralysis of the vocal cords. Among the illustrations omitted is one of Doctor Jackson performing a tracheotomy in an automobile (163c). There is the same list of references. An additional chapter has been added on War surgery of the Larynx. To all those interested in the diseases of the Larynx this edition is recommended as whole heartedly as was the previous one.

E. N. B.

Pleuro-subpleural Zone. By J. SKLÁDAL. 103 pp. Illus. $2.75. Cambridge University Press; The Macmillan Company, 1942.

In an era when there seems to be a waning interest in the elaboration and improvement of the usual methods of physical diagnosis, it is a happy circumstance that a careful student of physical signs publishes a contribution such as "The Pleuro-subpleural Zone."

This monograph of Skládal based on observations made in Prague before the fall of Czechoslovakia, finished in Paris before the collapse of France, and published in English by the Cambridge University Press arouses interest and commands the attention of students of thoracic disease.

The author, proceeding from the thesis that many subacute and chronic infections of the pleura and lungs are localized often in the superficial alveoli and in the pleura overlying them, devised auscultatory and radiologic methods to discover these cortico-pleural changes. Considering increased pressure and other changes of intrathoracic kinetics due to sudden expiration to be the same as those produced by coughing, he substituted the former for the latter in the examination of the

chest. Utilization of "sharp and ample expiration" instead of noisy cough during auscultation of the chest caused audible doubling of the expiratory sound with a tubular quality of the second sound whenever there was consolidation of the cortical parenchyma of the lungs. A tubular timbre of the second sound (of glottic origin) and small crepitant or moist rales at the beginning of the expiratory duplication were found to be indicators of different stages of cortical infiltration. Although, in most instances, the roentgen ray disclosed shadows varying from a semitransparent veil like "sugar icing on cakes" with a conical shape if in the apical region to a better defined clouding of the parenchyma of the lungs if elsewhere, such changes were sometimes minimal or lacking so that pathological alterations in the periphery of the lungs were based solely on physical signs.

Doctor Skládal's observations are important. They seem to offer a reliable means of determining the presence of pleural lesions that may readily escape detection by the utilization of the methods employed generally.

C. R. A.

Principles of Microbiology. By FRANCIS E. COLIEN and ETHEL J. ODEGARD. 444 pp. Illus. $3.00. C. V. Mosby Company, St. Louis, 1941.

This is distinctly an elementary text book in medical microbiology. Although it includes more than is usually required for nurses' courses, it might well serve as a text book. It is not sufficiently complete for medical students nor would it serve as a manual for bacteriological technicians. It would serve very well for cultural courses in medical microbiology for college students.

The book is well written and the material is well chosen. It evidences experience and acquaintance with recent developments in microbiology by the authors.

J. H. B.

Microbes Which Help or Destroy Us. By PAUL W. ALLEN, D. FRANK HOLTMAN, and LOUISE ALLEN MCBEE. 540 pp. Illus. $3.50. C. V. Mosby Company, St. Louis, 1941.

It is an art to write, on this subject, a book which has popular appeal and may also elicit the approval of serious scholars in the field. This is such a book. The subject presents a temptation for sensationalism. This the authors have avoided. Interest is inspired and perspective is attained by the first two chapters on Microbes and the Age of Science and The Age of Superstition. These are excellent and sufficiently restrained; the reviewer feels that much more could have been said, but probably at the expense of arousing prejudice. To the open-minded the continuation of the theme must be obvious.

The succeeding chapters are devoted to factual and interesting accounts, first of historical developments in bacteriology and then of various microbial agents of disease and of industrial processes, the two sometimes related.

The book should be profitable reading for the layman and as a supplemental text for students in general bacteriology, nursing and medicine.

J. H. B.

Modern Treatment of Syphilis. By JOSEPH EARLE MOORE. 2nd ed. 2nd printing. 717 pp. Illus. $7.00. Charles C. Thomas, Springfield, Illinois, 1943.

Since its first publication in 1933 this book has remained the outstanding treatise on the treatment of syphilis. The second edition, which appeared in 1941, was completely rewritten and greatly expanded with the assistance of the late Dr. J. E. Kemp and a number of other collaborators from the author's clinic at the Johns Hopkins University. In this second printing of the second edition the chapter on intensive arsenotherapy of early syphilis has been rewritten, and a new chapter on venereal disease control in the armed forces has been added.

The first four chapters of the book are devoted to a discussion of the fundamental biology of syphilitic infection in relationship to problems of treatment, to a consideration of the prognosis of treated and untreated syphilis, and to the appraisal of the therapeutic problem in the individual patient. In the next seven chapters each of the drugs employed in treatment, the reactions which they produce, and the technique of administration are discussed in detail.

There follow sixteen chapters on the management of various stages of syphilis—early, latent, cardiovascular, syphilis of the skin, bones and eyes, neurosyphilis, syphilis complicated by pregnancy and congenital syphilis. A chapter on the interpretation of serologic tests in diagnosis and treatment is included, and the last few chapters are devoted to a consideration of the public health aspects of syphilis.

Altogether this book provides the most comprehensive review of current knowledge concerning the treatment of syphilis, and the most authoritative guide to the principles and practice of syphilotherapy now available.

While changes in methods and techniques of treatment may be expected as the result of new discoveries and developments, it will be a long time before proven methods are discarded. The Modern Treatment of Syphilis can be regarded as indispensable to clinic directors and other specialists. In fact, no physician should attempt to treat syphilis without the background of knowledge so adequately provided in this book.

T. B. T.

BOOKS RECEIVED FOR REVIEW

Biological Symposia. Vol. X. *Frontiers in Cytochemistry.* Edited by JACQUES CATTELL. 334 pp. Illus. $3.50. Jacques Cattell Press, 1943.

The Compleat Pediatrician. By WILBURT C. DAVISON. 4th Ed. 256 pp. $3.75. Duke University Press, Durham, 1943.

Elementary Pharmacology and Therapeutics. By LUELLA C. SMITH. 2nd Ed. 300 pp. $2.00. The C. V. Mosby and Co., St. Louis, 1943.

Reconstructive Surgery of the Eyelids. By WENDELL HUGHES. 160 pp. Illus. $4.00. The C. V. Mosby and Co., St. Louis, 1943

Borderlands of Psychiatry. By STANLEY COBB. 166 pp. $2.50. Harvard University Press, 1943.

Oral Diagnosis. By KURT H. THOMA. 2nd Ed. 495 pp. Illus. $6.75. W. B. Saunders and Co., Philadelphia and London, 1943.

Methods of Treatment. By L. CLENDENING and E. HASHINGER. 8th Ed. 1033 pp. Illus. $10.00. The C. V. Mosby and Co., St. Louis, 1943.

Rehabilitation of the War Injured. By DOHERTY and RUNES. 684 pp. Illus. $10.00. Philosophical Library, 1943.

A Hundred Years of Medicine. By C. D. HAAGENSEN and W. LLOYD. 444 pp. Illus. $3.75. Sheridan House, New York, 1943.

Synopsis of Clinical Syphilis. By JAMES K. HOWLES. 671 pp. Illus. $6.00. The C. V. Mosby Co., St. Louis, 1943.

Manual of Fractures. By C. M. SHAAR and F. P. KREUZ, JR. 300 pp. Illus. $3.00. W. B. Saunders Company, Philadelphia and London, 1943.

Medical Clinics on Bone Diseases. By I. SNAPPER. 225 pp. Illus. $10.75. Interscience Publishers, Incs., New York, 1943.

The Ear, Nose and Throat in the Services. By R. STEVENSON. 116 pp. Illus. $1.50. Oxford University Press, 1943.

Geriatric Medicine. By E. J. STIEGLITZ. 887 pp. Illus. $10.00. W. B. Saunders Co., Philadelphia and London, 1943.

Essays in Biology. By HERBERT M. EVANS. 686 pp. Illus. $10.00. University of California Press, 1943.

An Introduction to Sociology and Social Problems. By DEBORAH JENSEN. 2nd Ed. 420 pp. Illus. The C. V. Mosby Company, St. Louis, 1943.

Medical Malpractice. By LOUIS J. REGAN. 256 pp. Illus. $5.00. The C. V. Mosby Company, St. Louis, 1943.

The Common Form of Niacin Amide Deficiency Diseases—Aniacinamidosis. By WM. KAUFMAN. 62 pp. $3.00. Bridgeport, New Haven, 1943.

Biology of Acarus scabiei. By R. FRIEDMAN. 183 pp. Illus. $3.00. Froben Press, New York, 1942.

Tifus Exantematico. By CLAVERO and GALLARDO. 166 pp. Illus. Madrid, 1941.

The Collected Papers of the Mayo Clinic. Vol. 34. 999 pp. Illus. $11.00. W. B. Saunders Company, Philadelphia and London, 1943.

Self-teaching Tests in Arithmetic for Nurses. By RUTH JESSEE. 111 pp. The C. V. Mosby Company, St. Louis, 1943.

The Vitamins. 99 pp. Illus. Frederick Stearns and Company, 1943.

Manometric Methods. By MALCOLM DIXON. 2nd Ed. 155 pp. Illus. $1.75. The Macmillan Company, New York, 1943.

Clinical Diagnosis by Laboratory Examinations. By J. A. KOLMER. 1239 pp. Illus. $8.00. D. Appleton-Century Co., 1943.

INDEX TO VOLUME LXXIII

Pagination According to Months:

July, 1943, pp. 1–64
August, 1943, pp. 65–142
September, 1943, pp. 143–237
October, 1943, pp. 239–305
November, 1943, pp. 307–399
December, 1943, pp. 401–495

Alcayaga, Raul (See Wintrobe, Maxwell M.)....169, 313
Alpern, E. Bryce, Nathaniel Finkelstein and Gantt, Horsley W.: Effect of Amphetamine (Benzedrine) Sulfate Upon Higher Nervous Activity.... 287
Amphetamine (Benzedrein) Sulfate, Effect of, Upon High Nervous Activity.... 287
Austrian, Charles R.: Lewellys Franklin Barker.... 401

Barker, Lewellys Franklin.... 401
Book Reviews....61, 140, 300, 396
Broyles, Edwin N., Comdr. (See Kenney, Edmund L.).... 479
Burnam, Curtis F.: Howard Atwood Kelly.... 1
Buschke, Wilhelm, Friedenwald, Jonas S. and Fleischmann, Walter: Studies on the Mitotic Activity of the Corneal Epithelium. Methods. The Effects of Colchicine, Ether, Cocaine and Ephedrin.... 143
Byrn, Jane Nicholls and Eastman, N. J.: Vitamin A Levels in Maternal and Fetal Blood Plasma.... 132

Choriomeningitis, Lymphocytic. Report of a Laboratory Infection.... 275
Ciliary Body, The Distribution of Certain Oxidative Enzymes in the.... 421
Cleidectomy, Scapulectomy and, in the Rat.... 223
Coburn, Alvin F.: Salicylate Therapy in Rheumatic Fever; a Rational Technique.... 435
Coburn, Alvin F. and Moore, Dan H.: The Plasma Proteins in Disseminated Lupus Erythematosus.... 196
Corneal, Studies on the Mitotic Activity of the, Epithelium. Methods. The Effects of Colchicine, Ether, Cocaine and Ephedrin.... 143

Deformal. A Simple Technique for Removing Formaldehyde from Preserved Tissue Specimens.... 138
Dingwall, James A., 3rd and Lord, Jere W., Jr.: The Fluorescein Test in the Management of Tubed (Pedicle) Flaps.... 129
Disseminated Lupus Erythematosus, The Plasma Proteins in.... 196

Eastman, N. J. (See Byrn, Jane Nicholls).... 132
Electrocardiographic Changes Associated with Thiamine Deficiency in Pigs.... 169
Elvers, Charles F.: Deformol. A Simple Technique for Removing Formaldehyde from Preserved Tissue Specimens.... 138
Estrogen, Attempt to Induce Formation of Fibroids with, in the Castrated Female Rhesus Monkey.... 23

Fibroids, Attempt to Induce Formation of, with Estrogen in the Castrated Female Rhesus Monkey 23
Fisher, A. Murray: The Antibacterial Properties of Crude Penicillin 343
Fleischmann, Walter (See Buschke, Wilhelm) 143
Fluorescein, The, Test in the Management of Tubed (Pedicle) Flaps 129
Follis, Richard H., Jr. (See Wintrobe, Maxwell M.) 169, 313
Ford, F. R. and Walsh, F. B.: Guillain-Barré Syndrome (Acute Infectious Polyneuritis) With Increased Intracranial Pressure and Papilledema. Report of Two Cases. 391
Friedenwald, Jonas S. (See Buschke, Wilhelm) 143
Friedenwald, Jonas, Herrmann, Heinz and Moses, Robert: The Distribution of Certain Oxidative Enzymes in the Ciliary Body 421

Golden, Alford (See Gregory, John E.) 408
Gregory, John E. (See Rich, Arnold R.) 239, 465
Gregory, John E., Golden, Alford, Haymaker, Webb: Mucormycosis of the Nervous System 408
Guillain-Barré Syndrome (Acute Infectious Polyneuritis) 391

Hayes, Guy S. and Hartman, Thomas L.: Lymphocytic Choriomeningitis 275
Hartman, Thomas L. (See Hayes, Guy S.) 275
Haymaker, Webb (See Gregory, John E.) 408
Hellmann, L. M. (See Wang, H. W.) 31
Herrmann, Heinz (See Friedenwald, Jonas) 321

Keeney, Edmund L.: The Fungistitic and Fungicidal Effect of Sodium Propionate on Common Pathogens 379
Keeney, Edmund L. and Broyles, Edwin N., Comdr.: Sodium Propionate in the Treatment of Superficial Fungous Infection 479
Kelly, Howard Atwood 1
Kunkel, Henry G. (See Oppenheimer, Ella H.) 40

Lord, Jere W., Jr. (See Dingwall, James A., 3rd) 129

Malaria, Cerebral—A Case Report 265
Moore, Dan H. (See Coburn, Alvin F.) 196
Moses, Robert (See Friedenwald, Jonas) 421
Mucormycosis of the Central Nervous System 405

Oppenheimer, Ella H. and Henry G. Kunkel: Further Observations on the Lowering of Blood Uric Acid By Uricase Injections 40
Oxidative Enzymes, The Distribution of Certain, in the Ciliary Body 421

Pantothenic Acid Deficiency in Swine 313
Paulson, M. (See Wintrobe, Maxwell M.) 313
Penicillin, Crude, The Antibacterial Properties of 343
Placenta, Studies in the Metabolism of the Human. I. Oxygen Consumption in Relation to Ageing 31
Plasma Proteins, The, in Disseminated Lupus Erythematosus 196

(Polyneuritis, Acute Infectious) Guillain-Barré Syndrome 391
Pratt, Loring W.: Scapulectomy and Cleidectomy in the Rat 223
Proceedings of the Meeting of the Johns Hopkins Medical Society 54

Rheumatic Carditis, Experimental Evidence that Lesions with the Basic Characteristics of, Can Result from Anaphylactic Hypersensitivity 239
Rheumatic Fever, Salicylate Therapy in; a Rational Technique 435
Rheumatic Pneumonitis, On the Anaphylactic Nature of 465
Rich, Arnold R. and Gregory, John E.: On the Anaphylactic Nature of Rheumatic Pneumonitis 465
Rich, Arnold R. and Gregory, John E.: Rheumatic Carditis, Experimental Evidence that Lesions with the Basic Characteristics of, Can Result from Anaphylactic Hypersensitivity 239
Rose, Jerzy E. and Clinton N. Woolsey: A Study of Thalamocortical relations in the Rabbit 65

Salicylate Therapy in Rheumatic Fever; a Rational Technique 435
Scapulectomy and Cleidectomy in the Rat 223
Shackelford, Richard T. and Whitehill, Richard: Successful Ligation of the Left Common Iliac Vein for Thrombophlebitis Complicated by Pulmonary Emboli .. 307
Sodium Propionate, The Fungistatic and Fungicidal Effect of, on Common Pathogens. 379
Sodium Propionate in the Treatment of Superficial Fungous Infections 479
Successful Ligation of the Left Common Iliac Vein for Thrombophlebitis Complicated by Pulmonary Emboli 307

Thalamo-cortical Relations, A Study of, in the Rabbit 65
Thiamine Deficiency, Electrocardiographic Changes Associated with, in Pigs 169

Uric Acid, Further Observations on the Lowering of Blood, by Uricase Injections ... 40

Vargas, Luis, Jr.: Attempt to Induce Formation of Fibroids with Estrogen, in the Castrated Female Rhesus Monkey 23
Vitamin A Levels in Maternal and Fetal Blood Plasma 132

Wang, H. W. and L. M. Hellman: Studies in the Metabolism of the Human Placenta. I. Oxygen Consumption in Relation to Ageing 31
Whitehill, Richard, Captain, Medical Corps, Army of the United States: Cerebral Malaria—A Case Report 265
Whitehill, Richard (See Shackelford, Richard T.) 307
Wintrobe, Maxwell, M., Follis, Richard H., Jr., Alcayaga, Paul, Paulson, M. and Humphreys, Stewart: Pantothenic Acid Deficiency in Swine. With particular reference to the effects on growth and on the alimentary tract 313

Basis for many uses

The pharmacologic actions of Luminal have been applied with great advantage in the clinical management of a variety of conditions and disorders . . . This well established drug exerts a sedative, hypnotic, antispasmodic and anticonvulsant effect . . . The desired result is often only a matter of dosage . . . Continued freedom from symptoms, as in epilepsy, may be obtained by the determination of the suitable maintenance dose in individual cases.

Write for informative booklet containing detailed clinical information and helpful dosage table.

How Supplied

LUMINAL TABLETS
¼, ½ and 1½ grains.

LUMINAL ELIXIR
¼ grain per teaspoonful

LUMINAL SODIUM TABLETS
¼, ½ and 1½ grains for oral use.

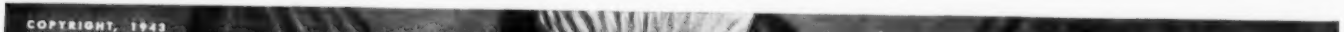
LUMINAL SODIUM AMPULS
2 and 5 grains for injection.

LUMINAL
Trademark Reg. U. S. Pat. Off. & Canada
Brand of
PHENOBARBITAL

Prices radically reduced

WINTHROP
CHEMICAL COMPANY, INC.
Pharmaceuticals of merit for the physician
NEW YORK 13, N. Y. WINDSOR, ONT.

COPYRIGHT, 1943
MEAD JOHNSON & CO.
EVANSVILLE, IND., U.S.A.
PABLUM
PABENA


COPYRIGHT, 1943